Check for updates

CORRESPONDENCE

REVISED Evidence for adverse effects of cannabidiol (CBD) products and their non-conformity on the European food market – response to the European Industrial Hemp Association [version 2; peer review: 2 approved]

Previously titled: "Evidence for side effects of cannabidiol (CBD) products and their non-conformity on the European food market – response to the European Industrial Hemp Association"

Dirk W. Lachenmeier , Stephan G. Walch

Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Karlsruhe, 76187, Germany

v2 First published: 26 Aug 2020, 9:1051
<https://doi.org/10.12688/f1000research.26045.1>
 Latest published: 16 Aug 2021, 9:1051
<https://doi.org/10.12688/f1000research.26045.2>

Abstract

An interesting and valuable discussion has arisen from our recent article (Lachenmeier et al., 2020) and we are pleased to have the opportunity to expand on the various points we made. Equally important, we wish to correct several important misunderstandings that were made by Kruse and Beitzke (2020) on behalf of the European Industrial Hemp Association (EIHA) that possibly contributed to their concerns about the validity of our data, toxicological assessment and conclusions regarding regulatory status of cannabidiol (CBD) products. First and foremost, our study did only assess the risk of psychotropic Δ^9 -tetrahydrocannabinol (THC) without inclusion of non-psychotropic Δ^9 -tetrahydrocannabinolic acid (THCA). Secondly, as this article will discuss in more detail, there is ample evidence for adverse effects of CBD products, not only in paediatric patients, but also in adult users of over-the-counter CBD products (including inadvertent "high" effects). Thirdly, the exposure and risk assessment was conducted using up-to-date guidelines according to the European Food Safety Authority (EFSA) and the German Federal Institute for Risk Assessment (BfR). And finally, the current legal situation in the European Union, without approval of any hemp extract-containing product according to the Novel Food regulation, actually allows blanket statements that all such products are illegal on the market, and this indeed would imply a general ban on the use and marketing of such products as food or food ingredients until such an approval has been granted. We hope that this reassures the F1000Research readership regarding the validity of our results and conclusions. We are pleased, though, that the EIHA has acknowledged

Open Peer Review

Approval Status

	1	2
version 2 (revision) 16 Aug 2021		
version 1 26 Aug 2020	 view	 view
<ol style="list-style-type: none"> Patrick John O'Mahony, Food Safety Authority of Ireland, Dublin, Ireland Katarina Cerne , University of Ljubljana, Ljubljana, Slovenia Tomaž Pezdir, University of Ljubljana, Ljubljana, Slovenia 		
Any reports and responses or comments on the article can be found at the end of the article.		

the fact that there are non-compliant CBD products available, but according to our data these are a substantial fraction of the market.

Keywords

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

This article is included in the [Agriculture, Food and Nutrition](#) gateway.

Corresponding author: Dirk W. Lachenmeier (lachenmeier@web.de)

Author roles: **Lachenmeier DW:** Conceptualization, Data Curation, Formal Analysis, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; **Walch SG:** Resources, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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

Copyright: © 2021 Lachenmeier DW and Walch SG. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Lachenmeier DW and Walch SG. **Evidence for adverse effects of cannabidiol (CBD) products and their non-conformity on the European food market – response to the European Industrial Hemp Association [version 2; peer review: 2 approved]** F1000Research 2021, 9:1051 <https://doi.org/10.12688/f1000research.26045.2>

First published: 26 Aug 2020, 9:1051 <https://doi.org/10.12688/f1000research.26045.1>

REVISED Amendments from Version 1

The text was revised considering the two reviews. Specifically, a figure showing a chromatogram of cannabinoid separation was added, and a discussion about the limitations of exposure assessment was implemented into the section about “THC” definition and estimation of daily dose of products. The section about the proposal of a legal ban on hemp extracts was updated considering recent regulatory developments.

Any further responses from the reviewers can be found at the end of the article

Introduction

We actually agree with a main premise of the European Industrial Hemp Association (EIHA)’s comments; namely, that legal compliance and safety for both producers and consumers of cannabidiol (CBD) products must be ensured¹. If this can be achieved by their suggestion of a mandatory industry self-regulated approach¹ rather than by our suggestion of strict regulations^{2,3} is another question. In light of the experience with industry self-regulations in other fields, this suggestion remains highly doubtful^{4,5}; it especially appears not well-thought-out how a self-regulation may be mandatory and how this demand can be enforced. Otherwise, we had previously suggested the necessity for a common regulatory approach regarding hemp food products on a European level, such as enforceable maximum levels for Δ^9 -tetrahydrocannabinol (Δ^9 -THC)⁶. To even increase the legal void by the assessment of hemp extract-based food products as non-foods within the international and national narcotic regulations⁷ is clearly not helpful.

Apart from these issues, which are political rather than scientific, the main finding presented in our study is that the levels of psychoactive Δ^9 -THC in many CBD products on the market exceed acceptable thresholds of toxicity. Furthermore, hemp extract-based CBD products were assessed as unapproved novel foods. For both reasons, the marketing of such products is illegal according to European Union (EU) food laws² (if we assume that the products are foods and not narcotics). The disputation provided by EIHA to refute our assessment is based on claims rather than facts and we therefore take this chance to corroborate our assessment by further data published since the last revision of our paper in January 2020.

Let us now consider each criticism of the EIHA¹ in detail:

Adverse effects of CBD products

The literature regarding adverse effects of CBD was considerably expanded since the writing of our article, so that besides the anecdotal reports and paediatric studies already mentioned, several case reports^{8–10}, a survey⁹, a meta-analysis of clinical trials¹¹ and a post marketing safety assessment of a full spectrum hemp extract¹² became available. Specifically the survey⁹ reports observations of adverse effects including “feeling high”, an effect likely to be explained by Δ^9 -THC contamination rather than by CBD. Similarly, effects of “a little high”, brief periods of mild intoxication, were described following ingestion

of several brands of CBD products in Virginia, USA¹⁰. The post marketing safety assessment showed gastrointestinal effects as most commonly reported adverse effect¹². We have included this information and several more studies into the two newer versions (version 3; v3¹³ and version 4; v4¹⁴) of our article² to strengthen our arguments. Besides the mentioned human evidence, experimental research *in vivo* and *in vitro* resulted in concerns about hepatotoxicity¹⁵, teratogenicity¹⁶, and gut inflammation¹⁷.

The arguments of EIHA in refuting any adverse effects of CBD products are not convincing not only from a pharmacological standpoint, but it is also rather unscientific to refute adverse effects on the basis that the responsible authority in the UK has not been made aware of any safety incident till now¹. First, due to the very short time of public use of CBD, only acute toxic events would currently appear, while chronic toxic events, such as liver toxicity, may take years to develop. Second, there is currently no system of nutrivicilance implemented in the UK or most other EU member states, so that there is no formal registration of such cases.

“THC” definition and estimation of daily dose of products

Unfortunately, a misunderstanding regarding our definition of Δ^9 -THC has apparently occurred at EIHA. From the methods section and our definition of the abbreviation of THC as Δ^9 -tetrahydrocannabinol, it should be clear that we only include the psychotropic Δ^9 -THC and not the non-psychotropic Δ^9 -tetrahydrocannabinolic acid (THCA) in our risk assessment. Both compounds are baseline separated in our chromatographic conditions (Figure 1).

In deviation of the suggested practice to implement the former German guidance values for total THC (i.e. the sum of Δ^9 -THC and THCA)¹⁸, we only have compared the psychotropic Δ^9 -THC with the guidance values. This practice is clearly in favour of the food business operator (FBO) because – as the EIHA correctly states – a major part of total THC may be comprised by THCA¹. We have updated our article to clarify this issue on several instances and to avoid future misunderstandings¹³.

Besides the issue about THCA and its potential degradation into Δ^9 -THC, the uncertainties and limitations of the exposure assessment include a lack of knowledge about the typical consumption amounts of hemp foods, which are not covered by the currently available representative nutritional surveys as a separate food category. This problem is less problematic for food supplements, which must be labelled with a recommended daily intake, but may lead to uncertainties with tea, beverages and other derivative products containing CBD or hemp extracts. The typical approach in such situations is to use survey data for the most similar food category (such as herbal tea for hemp tea, see detailed discussion in the examples below). Otherwise, to ensure a high level of consumer protection, worst-case consumption amounts, considering also sensitive consumer groups such as children, are typically considered in these situations.

Figure 1. Typical liquid chromatography-tandem mass spectrometry chromatogram of a cannabinoid mixture showing the separation between CBD (a), CBN (b), Δ^9 -THC (c), Δ^8 -THC (d) and THCA (e) (concentration 200 $\mu\text{g/L}$; analytical conditions see Ref. 14).

Regarding the exposure assessment, we confirm to have conducted an estimation of the daily intake in those instances, where a maximum recommended daily dose was missing in the labelling. This is in accordance with the requirements of Art. 14 of Regulation (EC) No. 178/2002 laying down the general principles and requirements of food law¹⁹, which specifies that the information provided to the consumer must be considered in determining whether any food is unsafe. As we will elaborate further in the following, our exposure estimations are both practical and realistic from the standpoint of consumer health protection.

Tea products (hemp flowers or leaves)

The authors consider 8 g of tea product consumption per day as an absolutely common and realistic scenario, e.g. comparable to consuming 1 teapot (for example 8 g infused in 1 L of water). The German Federal Institute for Risk Assessment (BfR) even suggests a slightly higher amount of 2 g / 200 mL infusion (10 g/L) and suggests that the actual acute consumption quantities for herbal tea as an analogon for hemp tea are in the order of 1.3 litres (P95)²⁰. Regarding the question of carry-over of THC into the infusion, the BfR has recently reviewed the evidence including the study cited by EIHA²¹ and another study by our group²². The BfR concluded: “The BfR is of the opinion that the assumption of 100% carryover is justified, as experimental data on the carryover point to high fluctuations”²⁰.

Therefore, we currently fail to see the evidence to change our exposure assessment for tea. Perhaps the EIHA can submit their unpublished test reports (see footnote 10 in Kruse & Beitzke¹) to the BfR for re-evaluation of their opinion, or even preferably make them publicly available in the form of a dataset for their article¹.

Finally, the allegation of the EIHA that we “ignored or overruled” the recommended daily dose on the label or the brewing instruction of the FBO¹ is untrue, as we certainly used this information when available (see dataset²³).

Syrup with hemp flower extract

According to the labelling, the syrup is intended to be used to prepare a beverage in 1:10 dilution with water. According to the BfR recommendation for tea, we assumed the use of 130 ml syrup to prepare 1.3 L of final beverage. The consumption of this amount of alcohol-free beverage is certainly not excessive nor is our assumption arbitrary or results-oriented. We would like to explicitly reject this unscientific and unfounded accusation of the EIHA¹ that the CVUA Karlsruhe or its employees’ work is results-oriented, in the sense that we exaggerate the risk of hemp products aiming to prohibit them from the market. On the contrary, the CVUA Karlsruhe works in its expert activities completely independent from any interests and our highest goal is the protection of the consumer from health damage.

Cannabis shot

There appears to be a misunderstanding about what is a “shot”. A shot is a form of concentrated beverage to be consumed as such and it is not a food supplement. The flask contains a single whole portion of the “shot” intended by the manufacturer to be consumed at once (e.g. compare “shots” of energy drinks). The “shot” is therefore clearly a “ready-to-eat” product.

CBD oil

Regarding the evaluation of so-called CBD oils, which are typically constituted of full spectrum hemp extracts mixed into edible oils to achieve CBD concentrations in the range 5–15% being sold as food supplements, the allegation of EIHA that we dismiss the many cases in which the dosage or recommended daily intake was provided correctly by the respective manufacturers¹, must be clearly rebutted. As can be seen in our dataset²³, as well as in Table 2 of our article², we have consistently and unambiguously used the labelled dosage of the manufacturers for the comparison with the toxicological thresholds. Naturally, for the products where no dosage had been labelled, exposure had to be estimated similar to the estimation for the beverages discussed above.

The product under specific scrutiny of EIHA is a special case as it was only labelled as “CBD oil” with no labelling suggesting it to be a “food supplement”. Therefore, the discussion regarding what consumers might expect from food supplements is not helpful. We believe that consumption of 10 ml (about 1 tablespoon) of an oil that is not labelled as “supplement” or with any other warning labels, is not an exaggerated or unrealistic scenario in all objectivity. It must also be considered that the THC content in this product was so high, that the consumption of 1/10 of the amount (i.e. 1 mL) would also exceed the lowest observed adverse effect level (LOAEL) and therefore lead to the same outcome. Nonetheless, we have clarified footnote 2 in Table 2 in the v3 of our article¹³ expanding the explanation of our exposure assessment in this case. It must be noted, however, that even if we would exclude this clearly exceptional and outlying product from our sample collective, all results and conclusions of our article are still valid. We are also surprised that the EIHA takes offence in our activities and responsibilities as part of governmental food control in Germany, while the problem clearly lies with FBOs that mislabel and misrepresent their products. Furthermore, for each of the products in Table 2 of our article², detailed expert opinions were produced for the responsible food control authorities that had initially submitted the samples to our institute. In some cases, our expert opinions have become part of court proceedings and the courts have confirmed the risk assessment of the CVUA Karlsruhe, as well as the risk management measures of the authorities in all cases known to date^{24–26}.

Mitigation of THC effects by interaction with CBD?

The allegation of EIHA that we have dismissed the interaction between THC and CBD¹, in the sense that CBD would mitigate the effects of THC, can be clearly rebutted. First and foremost, the underlying risk assessment in our expert opinions is based on the opinion of the Panel on Contaminants

in the Food Chain of the European Food Safety Authority (EFSA)²⁷, which has considered interaction effects. However, EFSA concluded the information is controversial and not consistently antagonistic²⁷. This is consistent with more recent research of Solowij *et al.*²⁸ that the effects of Δ^9 -THC may even be enhanced by low-dose CBD (e.g., as found in food supplements) and may be particularly prominent in infrequent cannabis users. Positive findings regarding antagonistic effects (e.g. Pisanti *et al.*²⁹ cited by EIHA) were typically found for much higher dosing regimens, i.e. aiming to mitigate the adverse effects of THC in hashish and marihuana, while another study with smoked cannabis did not detect such an effect³⁰.

We strongly believe, in line with EFSA, that the current scientific evidence does not allow for considering cumulative effects in low dose CBD oils and hemp extracts. The applicability and appropriateness of the acute reference dose (ARfD) of 1 μ g Δ^9 -THC per kg body weight – without considering interactions by CBD – was recently re-confirmed by EFSA³¹.

As the EIHA mentioned this argument, we have decided to include a short rationale into the v3 of our article¹³ for reasons of completeness. Otherwise, our article is not a basic toxicological research article about the rationale for risk assessment but an applied research article, which has based the risk assessment on the guidelines of the responsible risk assessment authorities BfR²⁰ and EFSA^{27,31}. Therefore, we would invite EIHA to correspond directly with these institutions, when they believe there is scientific evidence or new data that might change the available assessments. Currently, we see no such data. It should be noted that the EIHA has unsuccessfully tried lobbying the risk assessment bodies into providing more “reasonable” guidance values for THC (e.g., see Banas *et al.*³²), and we believe that a comment on our scientific article is not the right place to continue this effort.

Illegality of all hemp products containing isolated CBD or hemp extracts

While the regulatory status is not part of our chemical and toxicological research, we thank the EIHA for pointing out this issue, as there is a potential misunderstanding of the lobbyist regarding the most up-to-date regulations and decisions of EU and national legislators as well as of the courts, which is evidenced by the outdated references cited by EIHA¹.

We also thank the EIHA¹ for the re-iteration of our conclusion that “basically all available CBD products based on hemp extract marketed as food or food supplement within the EU are therefore illegally sold”. We still stand by this conclusion.

It is certainly true that case-by-case decisions have to be conducted in official food control, and of course we have exactly done this for each product, which was submitted to our laboratory for evaluation. However, the situation of hemp-extracts is a particular one, because of its regulatory status as unapproved novel food. This status allows for such a blanket statement, that each single product that contains hemp extract as ingredient can be judged as illegally placed on the

market. It should be noted that this assessment is independent of the amount of hemp extract or its concentration of CBD. Regarding the THC levels found, which are widely variable, a case by case decision has to be made in any case, which spans from unsuspecting levels below the ARfD up to exceedance of the LOAEL dose, which we judge as a serious risk in consideration of Art. 14 of Regulation (EC) No. 178/2002¹⁹.

The EIHA¹ is also correct in considering the EU Novel Food Catalogue, which leads to this “blanket” assessment of hemp extracts as being novel, as legally not binding and that it is only an indicator for court decisions. What the EIHA, however, fails to mention is the fact that there are a number of court decisions that have actually endorsed the suggestions of the novel food catalogue and have confirmed the actions of the authorities in prohibiting the placing of the respective CBD product on the market^{25,26,33–39}. To our knowledge, there currently is no court ruling, that might have endorsed the EIHA opinion.

Furthermore, the court rulings have also disproved the claims of the EIHA about the burden of proof for determining the novelty of a food. The opinion of EIHA¹ in this regard is based on outdated, incomplete evidence. In their decision about the marketability of a CBD product, the administrative court of the German Federal State Baden-Württemberg ruled that the food business operator has the burden of proof²⁶. This is in accordance with Article 4(1) of Regulation (EU) No 2015/2283, which states that the food business operator shall verify that foods which he or she has placed on the market in the EU, fall within the scope of this Regulation or not⁴⁰. Also outside the CBD field, the burden of proof has been imposed on the FBOs in several court rulings confirming Art. 4(1) of Regulation (EU) No 2015/2283 (see review of court rulings in Meyer *et al.*⁴¹). For a more detailed assessment of CBD court rulings see our recent review⁴².

Finally, we cannot follow the arguments of the EIHA¹ that European Court of Justice decisions regarding pharmacological effects might be relevant or that the novelty of a product is connected with an associated abstract health risk. The novelty of a product purely depends on the fact that it was not used for human consumption to a significant degree within the EU before 15 May 1997⁴⁰. The novelty does not depend on potential pharmacological effects or health risks of the product.

The German Federal Office of Consumer Protection and Food Safety (BVL) recently published a statement that the classification of food containing CBD in the press release of EIHA of March 3, 2020, is not correct⁴³. The BVL states that for extracts of *Cannabis sativa* L. and derived products containing cannabinoids (e.g. CBD) a significant history of consumption in the EU has still not been demonstrated by the economic operators, nor by the EIHA or any other association⁴³. For this reason, they are still considered EU-wide as novel foods⁴³.

In conclusion, we believe that the responsible authority can currently make conclusions on the non-marketability of CBD

products based on a lack of novel food approval, and additionally based on the lack of safety when THC thresholds are exceeded. We must stress here that the responsible local authority's tasks clearly include the enforcement of the Novel Food Regulation⁴⁰ as well of the food safety rules¹⁹. This is practiced all over Europe and evidenced by the numerous alerts found in the EU's Rapid Alert System for Food and Feed (RASFF)⁴⁴.

Judgement about food producers of CBD products

Since the publication of our article³, a number of studies have confirmed our analytical results. Food control authorities in Europe have reported various offences of FBOs selling CBD products against the European food law. More than 160 notifications regarding CBD as unauthorised novel food ingredient and/or unauthorised THC in CBD products were shared in the RASFF. In Belgium, about half of 213 products seized from CBD shops exceeded a threshold of 0.2% THC+THC-A and large discrepancies were observed between labelled and measured CBD concentration⁴⁵. The Food Safety Authority of Ireland (FSAI) reported that from 38 tested CBD products, 37% exceeded the safe limit of THC dosage set by EFSA (1 µg/kg body weight/day), 34% were classified as novel food lacking approval, 36% were food supplements lacking the necessary notification of the competent authority, 92% were tested to contain differences between analytical and declared CBD content of more than 10%, and finally 50% contained misleading claims such as unauthorised health claims or medicinal claims⁴⁶. An analysis of over-the-counter CBD products from the UK found that only 38% of 29 products were within 10% of advertised CBD content and 55% had measurable levels of THC or cannabiniol⁴⁷. Similarly, only 3 out of 25 CBD products from the State of Mississippi (USA) were within 20% of label claim, and 3 exceeded 0.3% THC⁴⁸. Similar studies from Italy⁴⁹, the Netherlands⁵⁰, and the USA⁵¹ are available.

In consideration of these consistent reports worldwide, we actually cannot find a better wording than our original statement: “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 risk.”

We fully stand by this conclusion and have even expanded our judgement of the CBD industry in a recent editorial, which concluded that the illegal market of CBD products may provide a strong rationale for the necessity of a paradigm shift towards pre-marketing approval in regulating food supplements³.

The following arguments of EIHA¹, starting with obsolete letters of the EU commission (written at a time when hemp extracts were not available on the market, highlighting their irrelevance to the current situation) and some disconnected information about novel food status, without providing any evidence at all besides unsubstantiated claims, cannot plausibly

refute our conclusions. Instead, we have provided ample evidence – based on EFSA criteria²⁷ – that a substantial number of CBD products on the market is not safe (69% of samples above ARfD of EFSA) and all samples (100%) were judged on a case-by-case basis as unapproved novel foods. Additionally, all samples (100%) were non-compliant with mandatory labelling rules and/or used unapproved health claims². We feel that this is ample proof for our statement above, which is based on facts.

The CVUA Karlsruhe as part of the food control system in the EU also clearly wishes to reject the allegation of EIHA¹ that the institute conducts “discrimination”, “undifferentiated action” and “arbitrariness”. We have assessed all products sent to our institute for evaluation in a transparent and consistent fashion (the criteria for evaluation were published in 2019⁵²), conducted our toxicological and regulatory assessment on a case-by-case basis², and even allowed public scrutiny by publishing our full dataset²³.

Regarding the concerns of EIHA to defend the reputable hemp industry against “free riders”, “black sheep” or “cowboys”, we can ensure them that food control includes this segment of the market as well, e.g. by conducting sampling of online stores. Otherwise, the EIHA has the possibility to take their own steps against such practices on the basis of the national laws against unfair commercial practices (e.g. in Germany “Gesetz gegen den unlauteren Wettbewerb (UWG)”).

The closing remarks of EIHA¹ in this section appear ill-considered. First, it is commendable that EIHA wants to ensure compliance with the law and consumer safety. But how can this solely be achieved by an industry standard? And how can an industry standard be made mandatory for all FBOs? Perhaps on a voluntary basis for the members of EIHA, but clearly not for the whole industry, and not for the “free riders”, “black sheep” or “cowboys”. As stated before, we would certainly agree with an improved legal basis for hemp food products similar to other vertical regulations in the food sector, such as the EU spirit drinks regulation. However, we fail to see how this can be achieved as an industry standard.

Regarding the lack of communication between EIHA and public authorities, we recall a technical discussion at our institute at the end of 2018 and are also aware that the EIHA was invited to present their evidence at the “Working Group Novel Food” in Brussels⁵³.

Finally, we congratulate the EIHA for the decision to facilitate novel food applications by conducting extensive toxicology studies.

Judgement of the hemp industry in the food sector

The quote “Currently CBD users must be aware that they may be ‘participating in one of the largest uncontrolled clinical trials in history’” of Pál Pacher included in a Newsweek article⁵⁴ is in our opinion very fitting to the reality of the

market. First, Pál Pacher is clearly an authority regarding cannabis research (e.g., Refs.^{55–58}). Second, the comment is regarding CBD and not regarding THC, and we currently cannot see a substantial difference between CBD content of food or nutritional supplements on the markets in the USA and Europe. Along with the lack of labelling detected in our study and the suggestions of many manufacturers to “gradually increase the dosage”, pharmacologically active CBD dosages similar to prescription medications may be easily reached by commercial over-the-counter CBD products on the market in Europe. As noted above, no nutrigenetics is typically conducted and no safety assessment has been conducted for the products, because the manufacturers put them on the market before achieving novel food approval. Nevertheless, according to the peer reviewer’s suggestion, we have removed the statement from article version 4; v4¹⁴).

Proposal of a legal ban on hemp extracts

We would like to note that we actually have suggested a regulated legalization of CBD products. Therefore, we question how or why the EIHA is interpreting this as the proposal of a “ban”. We also wonder why our statement “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 could be treated as illegal narcotics, prescription-based medicinal products, or novel foods” is criticized by the EIHA¹, when they actually provide supporting evidence with their examples of melatonin or garlic that certain substances could fall into either legal realm depending on labelling sometimes even when the concentration is similar (e.g., also compare sage tea⁵⁹ or *Ginkgo biloba* extract⁶⁰).

Our statement also has been validated by an assessment of the European Commission (according to press information⁷) to either consider hemp extracts as narcotics or as foods. As detailed elsewhere^{3,42}, we believe that it would be disproportional to regulate CBD products as narcotic drug according to the principle of “ultima ratio” in criminal law. Considering a decision by the Court of Justice of the European Union, the European Commission recently clarified its position to not further consider CBD as narcotic, but to advance the novel food approval procedure¹⁴.

Conclusions

We hope our response informs the F1000Research readership about the most recent evidence regarding the toxicological and regulatory evaluation of CBD products. We believe that the Correspondence article of the EIHA¹ has made many unsubstantiated claims and is unable to discredit our scientific work that was based on a validated and externally accredited analytical method² with fully transparent criteria for risk assessment based on BfR²⁰ and EFSA²⁷.

We hope that the promised extensive toxicological studies and quality standards of EIHA will include the following research questions:

- The deviation of the content of commercial CBD preparations from the labelling consistently found in studies worldwide (see above) could partially derive from instability of CBD during storage⁶¹. Research regarding stabilization of CBD appears necessary to ensure CBD stability during shelf-life.
- As a degradation of CBD is expected even in material from synthetic origin⁶², the degradation products must be identified and toxicologically assessed.
- Avoidance of THC contamination and adherence to food standards for THC.
- Toxicological assessment of CBD as food ingredient aiming to identify acceptable daily intakes without risk for the consumer or pharmacological effects. Currently,

there is no consensus of what constitutes a safe CBD dose, with recommendations ranging from as low as 4 mg/day⁶³ over 17.5 mg/day to 60 mg/day⁶⁴.

- Interactions between different compounds such as antagonistic or enhancing effects of the cannabinoid mixture contained in hemp extracts.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Acknowledgements

The authors would like to thank Patricia Golombek for providing the chromatogram of cannabinoids shown in [Figure 1](#).

References

- Kruse D, Beitzke B: **Comment on Lachenmeier *et al* (2020) "Are side effects of cannabidiol (CBD) products caused by tetrahydrocannabinol (THC) contamination?"**: disputation on various points in the publication [version 1; peer review: 1 approved]. *F1000Res*. 2020; 9: 900.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lachenmeier DW, Habel S, Fischer B, *et al.*: **Are side effects of cannabidiol (CBD) products caused by tetrahydrocannabinol (THC) contamination?** [version 2; peer review: 2 approved, 1 approved with reservations]. *F1000Res*. 2020; 8: 1394.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lachenmeier DW, Walch SG: **Cannabidiol (CBD): a strong plea for mandatory pre-marketing approval of food supplements.** *J Consum Prot Food Saf*. 2020; 15(2): 97–98.
[Publisher Full Text](#)
- Moodie R, Stuckler D, Monteiro C, *et al.*: **Profits and pandemics: prevention of harmful effects of tobacco, alcohol, and ultra-processed food and drink industries.** *Lancet*. 2013; 381(9867): 670–679.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Noel JK, Babor TF, Robaina K: **Industry self-regulation of alcohol marketing: a systematic review of content and exposure research.** *Addiction*. 2017; 112 Suppl 1: 28–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lachenmeier DW: **Hanfhaltige Lebensmittel – ein Problem?** *Deut Lebensm Rundsch*. 2004; 100(12): 481–90.
[Publisher Full Text](#)
- Gallen T: **EU CBD market under threat with narcotic classification favored.** HBW Insight, Informa Pharma Intelligence; 2020; (accessed on 22/07/2020).
[Reference Source](#)
- Yin HY, Hadjokas N, Mirchia K, *et al.*: **Commercial cannabinoid oil-induced Stevens-Johnson syndrome.** *Case Rep Ophthalmol Med*. 2020; 2020: 6760272.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bass J, Linz DR: **A case of toxicity from cannabidiol gummy ingestion.** *Cureus*. 2020; 12(4): e7688.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Pellerin C: **Getting high by mistake.** Healdsburg, CA, USA. Project CBD; 2020; (accessed on: 2020-08-10).
[Reference Source](#)
- Chesney E, Oliver D, Green A, *et al.*: **Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials.** *Neuropsychopharmacol*. 2020; 45(11): 1799–1806.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Schmitz SM, Lopez HL, Marinotti O: **Post marketing safety of Plus CBD™ products, a full spectrum hemp extract: A 2-year experience.** *J Diet Suppl*. 2020; 17(5): 587–98.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lachenmeier DW, Habel S, Fischer B, *et al.*: **Are side effects of cannabidiol (CBD) products caused by tetrahydrocannabinol (THC) contamination?** [version 3; peer review: 2 approved, 1 approved with reservations]. *F1000Res*. 2020; 8: 1394.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lachenmeier DW, Habel S, Fischer B, *et al.*: **Are adverse effects of cannabidiol (CBD) products caused by tetrahydrocannabinol (THC) contamination?** [version 4; peer review: 2 approved, 1 approved with reservations]. *F1000Res*. 2021; 8: 1394.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Walker LA, Koturbash I, Kingston R, *et al.*: **Cannabidiol (CBD) in dietary supplements: Perspectives on science, safety, and potential regulatory approaches.** *J Diet Suppl*. 2020; 17(5): 493–502.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Argueta DA, Ventura CM, Kiven S, *et al.*: **A balanced approach for cannabidiol use in chronic pain.** *Front Pharmacol*. 2020; 11: 561.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Skinner CM, Nookaew I, Ewing LE, *et al.*: **Potential probiotic or trigger of gut inflammation - The Janus-faced nature of cannabidiol-rich cannabis extract.** *J Diet Suppl*. 2020; 17(5): 543–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- BgVV: **BgVV empfiehlt Richtwerte für THC (Tetrahydrocannabinol) in hanfhaltigen Lebensmitteln.** Berlin: BgVV Pressedienst; 2000.
[Reference Source](#)
- European Parliament and Council: **Regulation (EC) No 178/2002 of the European Parliament and of the council of 28 January 2002 laying down the general principles and requirements of food law establishing the European Food Safety Authority and laying down procedures in matters of food safety.** *Off J Europ Comm*. 2002; L31: 1–24.
[Reference Source](#)
- BfR: **Tetrahydrocannabinol levels are too high in many hemp-containing foods - health impairments are possible.** BfR Opinion No 034/2018 of 8 November 2018. Berlin: Bundesinstitut für Risikobewertung; 2018; 2018.
[Publisher Full Text](#)
- Hazekamp A, Bastola K, Rashidi H, *et al.*: **Cannabis tea revisited: a systematic evaluation of the cannabinoid composition of cannabis tea.** *J Ethnopharmacol*. 2007; 113(1): 85–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lachenmeier DW, Kroener L, Musshoff F, *et al.*: **Determination of cannabinoids in hemp food products by use of headspace solid-phase microextraction and gas chromatography-mass spectrometry.** *Anal Bioanal Chem*. 2004; 378(1): 183–89.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Lachenmeier DW: **Dataset for "Are adverse effects of cannabidiol (CBD) products caused by delta9-tetrahydrocannabinol (THC) contamination?"** 2021.
[Publisher Full Text](#)
- OVG Lüneburg: **Beschluss vom 12. Dezember 2019 - 13 ME 320/19.** ECLI:DE:OVGNI: 2019: 1212: 13ME320.19.00; 2019.
- VG Freiburg: **Beschluss vom 21. Oktober 2019 - 10 K 2840/19.** 2019.
- VGH Baden-Württemberg: **Beschluss vom 16. Oktober 2019 - 9 S 535/19.** 2019.
- EFSA Panel on Contaminants in the Food Chain (CONTAM): **Scientific opinion on the risks for human health related to the presence of tetrahydrocannabinol (THC) in milk and other food of animal origin.** *EFSA J*.

- 2015; **13**(6): 4141.
[Publisher Full Text](#)
28. Solowij N, Broyd S, Greenwood LM, *et al.*: **A randomised controlled trial of vaporised Δ^9 -tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: acute intoxication effects.** *Eur Arch Psychiatry Clin Neurosci.* 2019; **269**(1): 17–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. Pisanti S, Malfitano AM, Ciaglia E, *et al.*: **Cannabidiol: State of the art and new challenges for therapeutic applications.** *Pharmacol Ther.* 2017; **175**: 133–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. Haney M, Malcolm RJ, Babalonis S, *et al.*: **Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis.** *Neuropsychopharmacology.* 2016; **41**(8): 1974–82.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 31. European Food Safety Authority (EFSA), Arcella D, Cascio C, *et al.*: **Acute human exposure assessment to tetrahydrocannabinol (Δ^9 -THC).** *EFSA J.* 2020; **18**(1): e05953.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 32. Banas B, Beitzke B, Carus M, *et al.*: **Reasonable guidance values for THC (Tetrahydrocannabinol) in food products. Position paper of the European Industrial Hemp Association (EiHA).** Hürth, Germany: European Industrial Hemp Association (EiHA); 2017.
[Reference Source](#)
 33. **VG Düsseldorf: Beschluss vom 27. September 2019 - 16 L 2333/19.** 2019.
[Reference Source](#)
 34. **VG Cottbus: Beschluss vom 08.01.2020 - 3 L 230/19.** ECLI:DE:VGCOTTB:2020:0108.3L230.19.00; 2020.
[Reference Source](#)
 35. **VG Hannover: Beschluss vom.** ECLI:DE:VGHANNO:2019:1118.15B3035.19.00; 2019.
[Reference Source](#)
 36. **VG Gießen: Beschluss vom 11. November 2019 - 4 L 3254/19.GI** 2019.
[Reference Source](#)
 37. **VG Stade: Beschluss vom 05. September 2019 - 6 B 735/19.** ECLI:DE:VGSTADE:2019:0905.6B735.19.00; 2019.
[Reference Source](#)
 38. **OVG Nordrhein-Westfalen: Beschluss vom 23.01.2020 - 13 B 1423/19.** 2020.
[Reference Source](#)
 39. **VG Schwerin: Beschluss vom 20.05.2020 - 7 B 394/20 SN.** 2020.
[Reference Source](#)
 40. European Parliament and the Council of the European Union: **Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001.** *Off J Europ Union.* 2015; **L327**: 1–22.
[Reference Source](#)
 41. Meyer AH, Rinke H, Verbeek U, *et al.*: **Neue Novel Food Verordnung 2015/2283, Fälle - Recht - Verfahren. 2. Auflage.** München: Eigenverlag – meyer.rechtsanwalts GmbH; 2019.
[Reference Source](#)
 42. Lachenmeier DW, Rajcic de Rezende T, Habel S, *et al.*: **Current case law confirms novel food classification of hemp extracts and cannabidiol (CBD) in foods – narcotic classification of cannabis foods remains unclear.** *Deut Lebensm Rundsch.* 2020; **116**(3): 111–19.
[Publisher Full Text](#)
 43. **BVL: Opinion of the BVL on the assessment of hemp extracts is unchanged.** Berlin, Deutschland Bundesamt für Verbraucherschutz und Lebensmittelsicherheit; 2020; accessed on: 2020-08-10.
 44. European Commission: **Rapid Alert System for Food and Feed (RASFF).** Brussels, Belgium. European Commission; 2020.
[Reference Source](#)
 45. Deville M, Dubois N, Denooz R, *et al.*: **Validation of an UHPLC/DAD method for the determination of cannabinoids in seized materials: Analysis of 213 samples sold in Belgian CBD shops.** *Forensic Sci Int.* 2020; **310**: 110234.
[PubMed Abstract](#) | [Publisher Full Text](#)
 46. **FSAI: Consumers being put at risk and misled with some CBD food supplements.** Food Safety Authority of Ireland; 2020. (accessed 18 March 2020).
[Reference Source](#)
 47. Liebling JP, Clarkson NJ, Gibbs BW, *et al.*: **An analysis of over-the-counter cannabidiol products in the United Kingdom.** *Cannabis Cannabinoid Res.* 2020; in press.
[PubMed Abstract](#) | [Publisher Full Text](#)
 48. Gurley BJ, Murphy TP, Gul W, *et al.*: **Content versus label claims in cannabidiol (CBD)-containing products obtained from commercial outlets in the State of Mississippi.** *J Diet Suppl.* 2020; **17**(5): 599–607.
[PubMed Abstract](#) | [Publisher Full Text](#)
 49. Pavlovic R, Nenna G, Calvi L, *et al.*: **Quality traits of “cannabidiol oils”: cannabinoids content, terpene fingerprint and oxidation stability of European commercially available preparations.** *Molecules.* 2018; **23**(5): 1230.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 50. Hazekamp A: **The trouble with CBD oil.** *Med Cannabis Cannabinoids.* 2018; **1**(1): 65–72.
[Publisher Full Text](#)
 51. Bonn-Miller MO, Loflin MJE, Thomas BF, *et al.*: **Labeling accuracy of cannabidiol extracts sold online.** *JAMA.* 2017; **318**(17): 1708–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 52. Lachenmeier DW, Bock V, Deych A, *et al.*: **Hemp food products - an update.** *Deut Lebensm Rundsch.* 2019; **115**(8): 351–72.
[Publisher Full Text](#)
 53. European Industrial Hemp Association: **European Industrial Hemp Association asked by European Commission to advise on traditional or novel food status of hemp extracts.** (Press release 15 January 2019). Brussels, Belgium. European Industrial Hemp Association; 2019. (accessed 2020-08-19).
[Reference Source](#)
 54. Freedman DH: **High on the hype.** *Newsweek.* 2019; 30–41.
 55. Pacher P, Kogan NM, Mechoulam R: **Beyond THC and endocannabinoids.** *Annu Rev Pharmacol Toxicol.* 2020; **60**: 637–59.
[PubMed Abstract](#) | [Publisher Full Text](#)
 56. Pacher P, Kunos G: **Modulating the endocannabinoid system in human health and disease - successes and failures.** *FEBS J.* 2013; **280**(9): 1918–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 57. Pacher P, Batkai S, Kunos G: **The endocannabinoid system as an emerging target of pharmacotherapy.** *Pharmacol Rev.* 2006; **58**(3): 389–462.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 58. Rajesh M, Mukhopadhyay P, Batkai S, *et al.*: **Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy.** *J Am Coll Cardiol.* 2010; **56**(25): 2115–25.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 59. Walch SG, Tinzoh LN, Zimmermann BF, *et al.*: **Antioxidant capacity and polyphenolic composition as quality indicators for aqueous infusions of *Salvia officinalis* L. (sage tea).** *Front Pharmacol.* 2011; **2**: 79.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 60. Lachenmeier DW, Steffen C, el-Atma O, *et al.*: **What is a food and what is a medicinal product in the European Union? Use of the benchmark dose (BMD) methodology to define a threshold for “pharmacological action”.** *Regul Toxicol Pharmacol.* 2012; **64**(2): 286–95.
[PubMed Abstract](#) | [Publisher Full Text](#)
 61. Golombek P, Müller M, Barthlott I, *et al.*: **Conversion of cannabidiol (CBD) into psychotropic cannabinoids including tetrahydrocannabinol (THC): A controversy in the scientific literature.** *Toxics.* 2020; **8**(2): 41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 62. Citti C, Russo F, Linciano P, *et al.*: **Origin of Δ^9 -tetrahydrocannabinol impurity in synthetic cannabidiol.** *Cannabis Cannabinoid Res.* 2021; **6**(1): 28–39.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 63. Tallon MJ: ***Cannabis sativa* L. and its extracts: Regulation of cannabidiol in the European Union and United Kingdom.** *J Diet Suppl.* 2020; **17**(5): 503–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
 64. Marinotti O, Sarill M: **Differentiating full-spectrum hemp extracts from CBD isolates: Implications for policy, safety and science.** *J Diet Suppl.* 2020; **17**(5): 517–26.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status:

Version 1

Reviewer Report 07 October 2020

<https://doi.org/10.5256/f1000research.28744.r70380>

© 2020 Cerne K et al. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Katarina Cerne

Institute of Pharmacology and Experimental Toxicology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Tomaž Pezdir

Institute of Forensic Medicine, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

In this correspondence article, the authors, Lachenmeier *et al.*, attempt to clarify some points they made in their recent article entitled "Are side effects of cannabidiol (CBD) products caused by tetrahydrocannabinol (THC) contamination?" (version 3, 19 Aug 2020). The reason for this response is comments on this article that were made by Kruse and Beitzke (26 Aug 2020) on behalf of the European Industrial Hemp Association (EIHA). The main topic is the safety of cannabidiol (CBD) products as a food or food ingredient for consumers, especially in relation to the tetrahydrocannabinol (THC) content. We believe that this issue is worth clarifying, because consumer exposure to unsafe substances is of particular concern since the exposed population may include people of all ages, both sexes and in all states of health. This area is of additional interest due to the new EU Novel Food Regulation 2015/2283.

In order to understand the clarifications of Lachenmeier *et al.* (2020) in this correspondence, it is necessary first to read the comments of Kruse and Beitzke (2020) and the article of Lachenmeier *et al.* (2020).

Below are the main points of Kruse and Beitzke comments to which Lachenmeier *et al.* wish to respond:

- Regarding the misunderstanding of the "THC" definition of daily dose of products,

Lachenmeier *et al.* explain that it should be clear from the method section and their definition of the abbreviation of THC as Δ^9 -tetrahydrocannabinol that they only include psychotropic Δ^9 -THC ("pure" Δ^9 -THC) and not its precursor, non-psychotropic Δ^9 -tetrahydrocannabinolic acid (THCA), in their risk assessment.

From the description of the LC methods, it is obvious that the compounds were separated chromatographically. However, the mass spectrum does not show the difference (the parent masses of both TQS and QTOF are identical and, due to low fragmentation, the daughter ions are

mainly the same on both instruments). Only the retention times from the chromatographic system show the difference between the substances. It would therefore be useful to show the chromatograms and note the retention times for each substance.

EFSA also gives preference to assessing exposure to “pure” Δ^9 -THC based on the LC-MS method. When samples are analysed using GC-FID or GC-MS (without a preliminary separation step) Δ^9 -THC and Δ^9 -THCA cannot be separated, so results are reported as the sum of Δ^9 -THC/ Δ^9 -THCA. Additionally, EFSA considered 100 % conversion of THCA to THC. Such a report is thus expected to represent an overestimation of exposure to “pure” Δ^9 -THC for two reasons: the THCA content in hemp is usually higher than the THC content and it is not known to what extent THCA is converted to THC in food¹.

Kurse and Beitzke also comment on the very high daily dose of Δ^9 -THC in some products, e.g. tea products. Since this is an initial exposure assessment, it would be helpful if the authors were to describe major sources of uncertainties and the limitation of the exposure assessment in a separate paragraph.

- Side effects of CBD products

First, we would like to say that the term ‘side effect’ is inappropriate. Adverse or toxicological effect is a more appropriate term. However, we will use the term ‘side effect’ to avoid confusion. Since Kurse and Beitzke refuted any side effects of CBD, Lachenmeier *et al.* provided additional literature to the contrary. They proposed that the causes of the side effects are either a direct toxicological effect of CBD, the degradation of CBD to Δ^9 -THC due to acidic hydrolysis in the stomach following oral consumption or Δ^9 -THC directly contained in the products. A side effect such as “feeling high” is likely to be explained by Δ^9 -THC contamination rather than by CBD. In humans, gastrointestinal effects are the most commonly reported side effect. Non-clinical studies have resulted in concerns about hepatotoxicity, teratogenicity and gut inflammation. They have also emphasized that the absence of acute toxic events does not mean that there are no chronic effects. However, not enough time has elapsed since CBD extracts have been more widely present on the market for chronic effect to show up (e.g., chronic liver injury). In addition, the absence of serious side effects is not enough for current safety criteria. Moreover, there is currently no system of nutri-vigilance implemented, so there is no formal registration of such cases and such events may be unrecognized.

There are still many uncertainties and contradictions remaining from the increasing number of published cannabinoid safety studies. This is because these studies vary to the extreme in their methodology and quality, rendering results difficult to compare. Moreover, toxicity is not systematically covered, and there are no chronic toxicity data from well-defined exposure settings. Although Kurse and Beitzke criticize the usage of Epidiolex® as a reliable source of toxicological information on CBD, as a 99 % pure extract from *C. sativa*, CBD has become the most extensively toxicologically tested cannabinoid. In spite of the fact that Epidiolex® has been approved for treatment-resistant epilepsy, the non-clinical part of testing was independent of this indication². CBD is extensively metabolised in the liver and gut, mainly by the CYP2C19, CYP3A4, UGT1A7, UGT1A9, and UGT2B7 enzymes. The metabolism of CBD is very complex, especially in hepatocytes. The main human metabolite is 7-carboxy-cannabidiol (7-COOH-CBD; ~90 % of all drug-related substances measured in the plasma)³. Its toxicological profile has not been investigated because experimental animals for toxicological studies (mice, rats, and dogs) do not metabolise CBD to a comparable extent as do humans⁴. The major concern with 7-COOH-CBD may be its reactive acyl-glucuronide⁵. CYP-mediated interaction is one of the major concerns in clinical practice. Drug interaction trials to assess the effect of CBD on these enzymes in healthy volunteers will therefore be conducted during the post-marketing period. A full battery of non-clinical oral reproductive and

developmental studies has been conducted with purified CBD, showing toxicological effects². Since the novel food status of CBD extracts was confirmed in January 2019, the Food Standard Agency (FSA) has given CBD companies a deadline of March 31, 2020 to apply for authorisations of their CBD extracts and isolates (for each product). In this regard, toxicity testing should be systematically covered, so the safety of each of CBD product will be clear.

- Mitigation of THC effects by interaction with CBD

Lachenmeier *et al.* re-confirmed their risk assessment without considering the interaction with CBD, since the opinion of EFSA is that information on THC/CBD interactions is controversial and not consistently antagonistic. EFSA also re-confirmed their acute reference dose (ARfD) of 1 µg/kg body weight (BW), without considering the interaction with CBD. Additionally, Lachenmeier *et al.* provided reference to recent research of Solowij *et al.*, in which they found that the effects of Δ⁹-THC may even be enhanced by low-dose CBD.

In spite of its low affinity for CB₁ and CB₂ receptors, CBD can interfere with some THC adverse effects, particularly in the brain, without interfering with the intended THC effects, such as muscle relaxation⁶. In terms of the pharmacokinetic CBD/THC interaction, CBD may impair THC hydrolysis by the CYP450 enzyme⁷. The inhibition of THC metabolism may vary with species, timing of administration (CBD pre-administration vs co-administration), and CYP isoenzymes⁸. Whether CBD will antagonise or potentiate THC effects also seems to depend on their administration ratio, and this ratio varies with species. Given all these possibilities, prediction of interactions between THC and CBD in food can be quite a challenge, so we do not yet see the possibility of including them in the risk assessment of CBD products.

When using ARfD, it is necessary to consider that it represents an estimate of the amount of a substance in food that can be ingested, usually during one meal or one day. This has been established on the base of central nervous system effects and increased heart rate, which were noted at a low Δ⁹-THC level (2.5 mg/day) in humans and occurred within a short time after dose administration. This dose, corresponding to 0.036 mg/day/kg BW for a person with a body weight of 70 kg, was regarded as the lowest-observed-adverse-effect level (LOAEL) in both single and repeated studies. Using an uncertainty factor (UF) of 3 for extrapolation from the LOAEL to a no-observed-effect-level (NOAEL) and an UF of 10 for interindividual differences, an overall UF of 30 was established (0.036 mg/day/kg: 30 = 0.001 mg/day/kg) (1). When applying the UF, the recommended daily dose for adults is 0.07 mg. At a higher consumption level, there is a risk of influence on the person's ability to operate machinery and drive vehicles. Interestingly, Lachenmeier *et al.* used LOAEL in their assessment without applying UF.

- Illegality of all hemp products containing isolated CBD or hemp extracts

After the date mentioned above, only products that have a validated novel food application will be allowed to remain on the market. It is therefore our view that regulatory issues are very extensively written and could be less extensive and shorter.

References

1. European Food Safety Authority EFSA, Arcella D, Cascio C, Mackay K: Acute human exposure assessment to tetrahydrocannabinol (Δ⁹-THC). *EFSA J.* 2020; **18** (1): e05953 [PubMed Abstract](#) | [Publisher Full Text](#)
2. International non-proprietary name: cannabidiol. *European Medicines Agency.* 2019. [Reference Source](#)
3. Ujváry I, Hanuš L: Human Metabolites of Cannabidiol: A Review on Their Formation, Biological Activity, and Relevance in Therapy. *Cannabis Cannabinoid Res.* 2016; **1** (1): 90-101 [PubMed Abstract](#) |

[Publisher Full Text](#)

4. Harvey D, Samara E, Mechoulam R: Comparative metabolism of cannabidiol in dog, rat and man. *Pharmacology Biochemistry and Behavior*. 1991; **40** (3): 523-532 [Publisher Full Text](#)
5. Regan SL, Maggs JL, Hammond TG, Lambert C, et al.: Acyl glucuronides: the good, the bad and the ugly. *Biopharm Drug Dispos*. 2010; **31** (7): 367-95 [PubMed Abstract](#) | [Publisher Full Text](#)
6. Russo E, Guy GW: A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses*. 2006; **66** (2): 234-46 [PubMed Abstract](#) | [Publisher Full Text](#)
7. Bornheim LM, Kim KY, Li J, Perotti BY, et al.: Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. *Drug Metab Dispos*. 1995; **23** (8): 825-31 [PubMed Abstract](#)
8. Mechoulam R, Parker L: Towards a better cannabis drug. *Br J Pharmacol*. 2013; **170** (7): 1363-4 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the rationale for commenting on the previous publication clearly described?

Yes

Are any opinions stated well-argued, clear and cogent?

Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?

Partly

Is the conclusion balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Katarina Černe: experimental and clinical toxicology, pharmacology, cannabinoids, risk assessment. Tomaž Pezdir: analytical chemistry, forensic toxicology, cannabinoids

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

Author Response 11 Aug 2021

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

We thank the reviewers for the assessment of our article. Due to the requests, the following changes were implemented:

- A representative chromatogram with marked retention times for each substance was included.
- A short discussion about sources of uncertainties and limitations of exposure assessment was added to the section "THC definition and estimation of daily dose of

products”.

- The term “side effects” was changed to “adverse effects” as requested.
- Regarding the adverse effects of CBD products, we want to thank the reviewer for the insights and remarks on toxicology and metabolism of the compound. We found that this information was more appropriate for inclusion in our original article and have done so during our recent revision into v4 of the article¹.
- Regarding the application of ARfD and LOAEL for risk assessment, we want to point out that we are using both thresholds and not only the LOAEL. A food containing THC in exceedance of ARfD is considered as being “unfit for human consumption” (Article 14 No. 2 (b) of regulation (EC) No 178/2002), while a food containing THC in exceedance of LOAEL is considered as “injurious to health” (Article 14 No. 2 (a) of regulation (EC) No 178/2002). The distinction is also clearly marked by the colours in Table 2 (last column) of our original article¹. Furthermore, this distinction also leads to prioritization of risk management measures, e.g. in terms of urgency, inclusion in rapid alert system RASFF, etc.
- In conclusion, it must be noted that while having already passed the mentioned FSA deadline of March 31, 2021, no product has been approved so far in the UK, and none in the European Union as well. Therefore, we believe that our regulatory section is still valid, and we have refrained from shortening the section so far.

References

1 Lachenmeier DW, Habel S, Fischer B et al. Are side effects of cannabidiol (CBD) products caused by tetrahydrocannabinol (THC) contamination? [version 4; peer review: 2 approved, 1 approved with reservations]. F1000Research 2021, 8:1394 (<https://doi.org/10.12688/f1000research.19931.4>)

Competing Interests: No competing interests were disclosed.

Reviewer Report 07 September 2020

<https://doi.org/10.5256/f1000research.28744.r70375>

© 2020 O'Mahony P. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Patrick John O'Mahony

Food Safety Authority of Ireland, Dublin, Ireland

Side effects of CBD products - EU food regulators await the final opinion of EFSA on the safety assessment of synthetic CBD. Many claims are made about CBD, some health claims not authorised in the EU, some relating to the mitigating effect of CBD on THC (as yet unproven conclusively). World-wide reports of foods and supplements claiming to contain CBD show that a significant proportion also contain THC, some at unsafe levels and some at levels that could result

in the "high" associated with recreational cannabis use.

THC definition and estimation of daily dose of products - In some EU Member States (MS) there is a threshold for THC contaminants in food, but not in others. EU food law is categorical (Reg 178/2002) food does not include narcotics which means any THC in food is considered a contaminant for which there is as yet no safe limit designated. Some EU MS have developed national limits for THC in food and in the future there could be an EU threshold for THC as a contaminant in hemp seed food products (in development). In some MS police can and do remove food products from sale based on any THC level under national legislation.

Cannabis shot - I agree with the author here. Under food law, a supplement must declare a recommended and/or maximum dosage. A shot is generally considered a small amount of concentrated beverage (usually alcoholic) to be consumed in one go.

CBD oil - Supplements must declare a dosage by law. If not a supplement with no recommended usage guidance then it is anyone's guess as to appropriate use.

Mitigation of THC effects by interaction with CBD - This is not an argument for food law and has not been discussed by regulators. THC presence in food is not specifically permitted by food law and tolerance thresholds for THC as a contaminant are in effect in some EU MS only, with a possibility of an EU-wide threshold in the future. It is unlikely that any EU food regulatory authority would have such a discussion with the industry.

Illegality of all hemp products containing isolated CBD or hemp extracts - The novel food catalogue is not a legally binding document as stated. However, it does reflect the agreed outcome of discussions at the novel food working group and therefore is binding in so far as all MS agree to interpret and implement the conclusions accordingly within their jurisdictions. Industry groups have tried unsuccessfully to argue that hemp extracts were on the EU market prior to 1997. Any food or ingredient which is a purified/extracted/concentrated component of an existing (not novel) food is likely to be considered a novel food and this standard has been used for almost two decades with many different examples available. Court rulings in one MS have no bearing on the implementation or interpretation of food law in other MS. At most such national court rulings can result in a case being sent to the European Court of Justice (ECJ), the results of which may then necessitate EU-wide legislation consideration.

Novel food status is not based on safety or otherwise as stated by the author, but on a significant history of consumption in the EU before 1997.

Judgement about food producers of CBD products - The idea that registered CBD producers of hemp extracts would be allowed on the market was dismissed as an irrational proposal of industry regulation by this regulatory body. THC content is not the only regulatory or safety issue with hemp products on the market as pointed out by the author through the many reports cited.

Judgement of the hemp industry in the food sector - The statement in Newsweek about "the largest uncontrolled clinical trials in history" is in my opinion the type of histrionic argument used against GMOs and in other food and non-food areas over the years. The reality is that many foods on the market (particularly supplements) fly under the radar until caught by routine surveillance or by the manifestation of safety issues. Therefore, it could be said that there are many "large-scale uncontrolled clinical trials" ongoing around the world in food, cosmetics, etc. This sort of

inflammatory statement does not aid a rational discussion. There has been no reliable safety assessment yet of CBD ingestion and until then, safety levels of CBD or the hundred plus other cannabinoids in *Cannabis sativa* is unclear. A thorough safety assessment as being carried out by EFSA currently will address issues of safe intake levels, interactions of CBD with other cannabinoids or other foods. It will also address stability and breakdown products of cannabinoids like CBD.

Is the rationale for commenting on the previous publication clearly described?

Yes

Are any opinions stated well-argued, clear and cogent?

Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?

Yes

Is the conclusion balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am not a research scientist. I am a scientist (molecular biologist by training) working in the Irish/EU food regulatory arena for 20 years. I have been looking after the novel food area (among others) in Ireland for 20 years and have coordinated the analytical survey of the Irish market for hemp-products as published in February 2020.

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 11 Aug 2021

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

Thank you for your insightful remarks regarding the regulatory status of CBD. As requested, we have removed the histrionic argument from Newsweek in v4 of our article¹.

References

1 Lachenmeier DW, Habel S, Fischer B et al. Are side effects of cannabidiol (CBD) products caused by tetrahydrocannabinol (THC) contamination? [version 4; peer review: 2 approved, 1 approved with reservations]. F1000Research 2021, 8:1394 (<https://doi.org/10.12688/f1000research.19931.4>)

Competing Interests: none

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research