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MINI REVIEW

WILEY

A review of cannabidiol-containing electronic liquids—Current regulations and labelling accuracy

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Abstract

The use of cannabidiol in electronic liquids (e-liquids) is becoming increasingly widespread, and the current regulations enforced onto nicotine-containing e-liquids are not applicable to cannabidiol-based products. This has led to concerns about the quality of cannabidiol vapes. Articles investigating the reliability of product labelling were reviewed using systematic review criteria. Of 70 e-liquids, 77.1% of the e-liquids tested in the articles were found to have underestimated or overestimated the cannabidiol quantities stated in the product labelling. Statistical analysis confirmed that there was a significant difference between the labelled and analysed cannabidiol concentrations ($p < 0.05$, Mann-Whitney U and Wilcoxon Signed Rank). Inaccuracies in received cannabidiol dosages could lead to an increased risk of adverse reactions or limit the therapeutic effect received, highlighting the benefit of enforcing specific regulations on cannabidiol-based e-liquids to protect consumer safety and guarantee product efficacy.

KEYWORDS
cannabidiol, cannabinoids, electronic cigarettes, e-liquids, labelling

1 | INTRODUCTION

In 1965, Herbert A. Gilbert was granted a patent for the very first smokeless, tobacco-free cigarette.[1] Despite this, the first commercially successful electronic cigarette (EC) was not invented until 2003, by Hon Lik in Beijing as a safer alternative to traditional cigarettes.[2] This invention was hugely successful, and in 2019, the e-cigarette market was given an estimated value of £15.5 billion worldwide.[3] There is now a vast array of e-cigarette products available, both disposable and reusable devices in a variety of designs that can be modified by the user to fit their individual needs.[4] Even with such diversity, the main components of an e-cigarette remain the same: a battery, an atomiser and a cartridge.[2] The role of the battery is to power the atomiser, which generates the aerosol that the user inhales. The cartridge is filled with a solution, known as an e-liquid, that is composed of a mixture of propylene glycol and vegetable glycerin. In addition to this, they can contain varying amounts of nicotine and different flavourings.

Aside from nicotine, e-cigarettes are utilised as an efficient method of consumption for a range of other substances. E-liquids containing the cannabinoid, cannabidiol (CBD), have quickly grown in popularity and have become widely available for purchase from high-street retailers and online websites. CBD is a naturally occurring compound present in the *Cannabis sativa* plant that has gained recognition for its potential therapeutic effects including pain and anxiety relief.[5,6] A recurring concern expressed in the literature is a lack of quality control enforced on the production of CBD-enriched products.[7] The worrying consequences of these minimal regulations have been demonstrated through discrepancies found between analysed CBD contents and those stated on the packaging.[8] A survey revealed that e-cigarette users are not knowledgeable on the current status of regulations and therefore are unaware of the potential risks they are exposed to.[9]

2 | AIM AND SCOPE OF THE REVIEW

The aim of this review was to discuss whether the current regulations enforced onto cannabidiol enriched e-liquids are sufficient to guarantee product quality and consumer safety. It was also considered whether there are any dangers associated with the use of these products that would demand for stricter regulations. Articles relating to the CBD content of EC products were also reviewed according to systematic review criteria.

3 | METHODS

Information was gathered through internet searches and reading the available laws and circulars.[10] The search string used for labelling accuracy studies was cannabidiol AND e-liquid OR e-cigarette OR electronic cigarette. Scopus, Pubmed and Google Scholar were utilised in the search along with manual checking of reference lists to obtain all potential records (Figure 1). The searches were carried out up to October 2020.

To establish whether there was a statistically significant difference between the labelled and analysed CBD concentration, the Kolmogorov-Smirnov and Shapiro-Wilk tests were initially conducted to test for normality. The Mann-Whitney U test was used to explore significance by comparing the medians of advertised and measured CBD concentrations.

4 | LAWS CONCERNING E-LIQUIDS

Laws regarding e-cigarettes and their accessories are complex and continuously evolving. The extent of regulation and opinion towards vaping is widely varied across the globe. For example, in the United Kingdom (UK), the use of e-cigarettes as a cessation tool is encouraged,[11] whereas some countries, including Mexico and India, have issued complete bans on the import, distribution and sale of e-cigarettes due to safety concerns.[12,13] The reasons for the ban in Mexico are unclear as zero-nicotine e-liquid as well as hardware have also been banned but are likely due to be a result of recommendations by the World Health Organization. Major concerns include the potential addictive nature of the devices and secondary smoking from inhaling particulate matter, 1,2-propanediol, volatile organic compounds, heavy metals and nicotine.[12] In India, concerns were raised about the habitual use particularly among the youth, and e-cigarettes were banned to prevent use from reaching 'epidemic' proportions.[13]

As e-cigarettes are relatively new to the consumer market, numerous countries, including multiple African nations, have not yet amended their tobacco laws to incorporate vaporisation products within their definition of tobacco products. Therefore, e-cigarettes are not currently regulated in any capacity in these countries. In general, e-cigarettes are most likely to be prohibited in South America and Middle Eastern regions (Figure 2). However, the coverage of the enforced ban is not always uniform. The sale of products within Bhutan is banned, but products can be imported into the country,

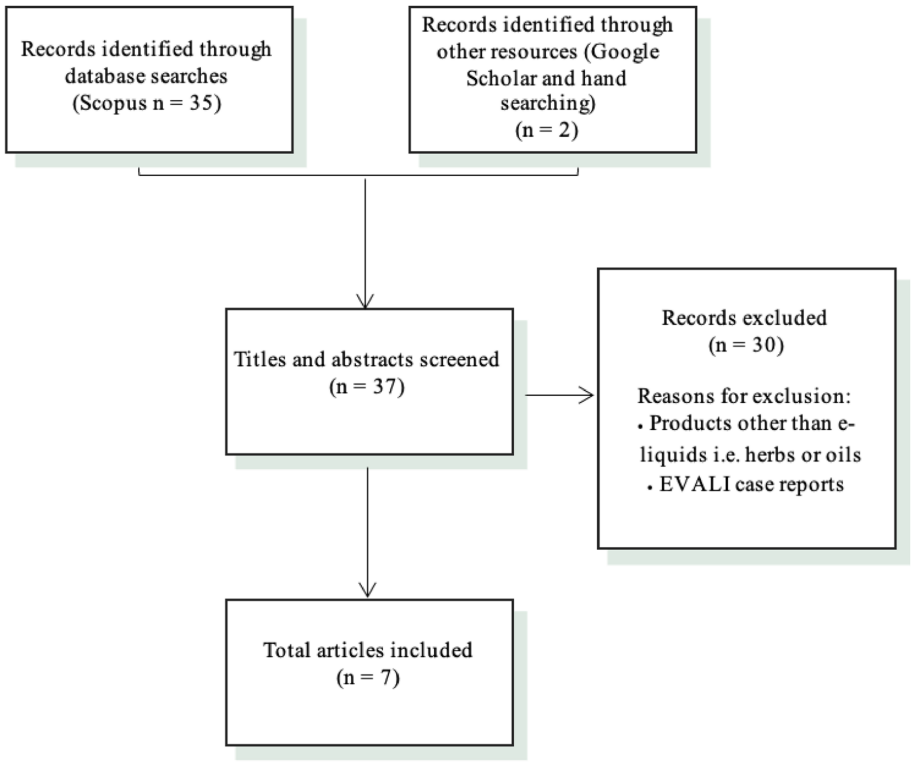


FIGURE 1 Flow chart of screening and selection process implemented to identify articles relevant to the mislabelling of cannabidiol e-liquids [Colour figure can be viewed at wileyonlinelibrary.com]

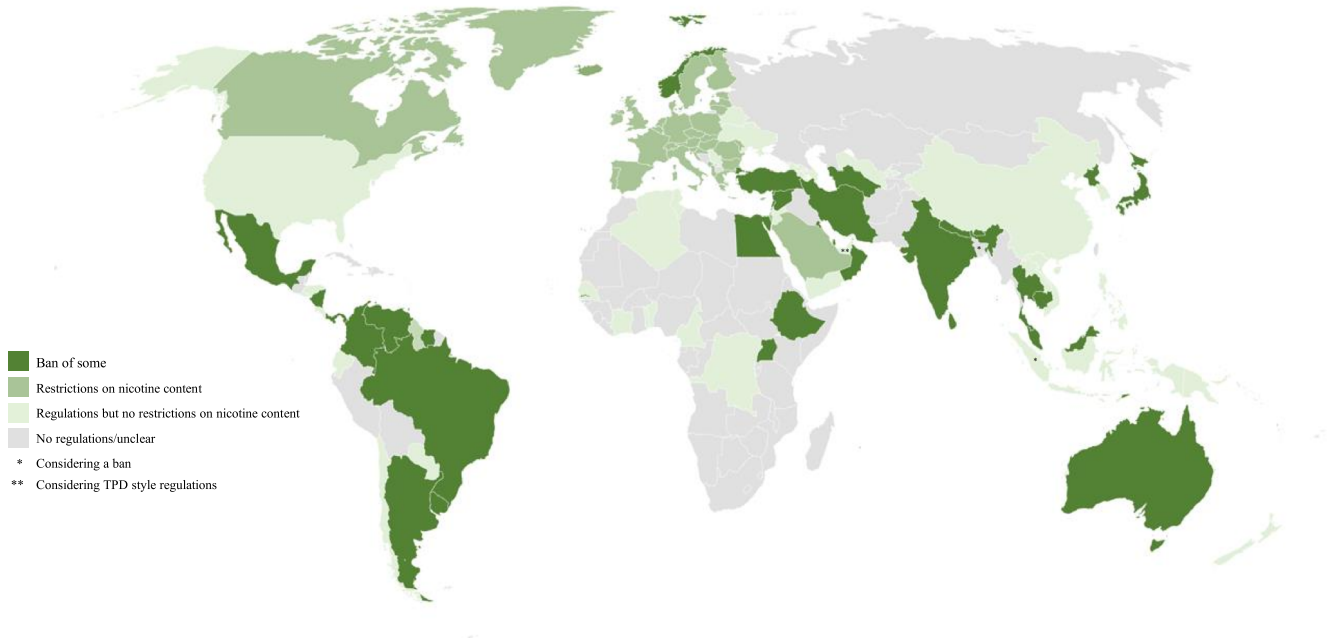


FIGURE 2 Current restrictions on electronic liquids worldwide as of may 2020. Countries indicated with a '*' are reported to be considering a ban, whilst '**' denotes countries which are considering adopting TPD style regulations, which would include a 20 mg/ml nicotine cap

whereas in Japan, there is a ban on products containing nicotine, but e-liquids without nicotine are unregulated.[14,15]

The Tobacco Products Directive (TPD) was established in 2001 as a means of introducing regulations on the manufacture and presentation of tobacco products for sale within the European Union.[16] In 2014, a revised directive was issued to incorporate e-cigarettes and e-liquids into these laws.[17] These rules stated that the nicotine content within a cartridge must be capped at 20 mg/ml. Various flavours and ingredients were banned such as caffeine or vitamins to prevent any association to energising effects or health benefits. This ban covered any stimulant compounds or additives yet nicotine, which is a stimulant drug, is still a permitted ingredient.

On 20 May 2016, these new rules came into force and all EU Member States have adopted the proposed regulations, but some states have implemented their own specific guidelines. Within the UK, the TPD is enforced by the Tobacco and Related Products Regulations 2016, but the Medicines and Healthcare Products Regulatory Agency (MHRA) have chosen to operate a Yellow Card Scheme.[18] Although the scheme had previously been used to document suspected adverse reactions to medicines and medical devices, in 2016, it was extended to encompass reporting of suspected adverse reactions to EC and e-liquids. In this system, side-effects as well as product safety concerns are reported. Between January 2015 and October 2017, 37 reports containing 99 suspected adverse reactions were documented, with the most common ailments including gastrointestinal complaints (such as nausea), respiratory ailments (such as cough) and headache.[18]

In comparison, the United States (US) has a lenient approach to e-liquid legislation. The Food and Drug Administration (FDA) began to regulate e-liquid packaging in 2018 to make it less appealing to minors.[19] There are currently no restrictions on the total volume or nicotine concentration in cartridges, but in January 2020, the FDA announced that enforcement against flavoured vapes would be made a priority.[20]

Whilst certain regions have implemented the necessary restrictions to ensure that these products are safe, most regulations are only applicable to nicotine-containing e-liquids. This generates complications for cannabidiol-based e-liquids, which predominantly do not contain any nicotine and therefore fall outside of the scope of these directives.

5 | LAWS ON CANNABIDIOL AND CANNABIDIOL E-LIQUIDS

The main legal requirement for any cannabidiol-based product is a cap on the quantity of the psychoactive cannabinoid, tetrahydrocannabinol (THC), present in the industrial hemp used in the manufacturing of these products. This cap creates confusion as the designated limit in each country is varied, ranging from 0% to 1% (Table 1).[22] Further, the implemented limits are not permanent, as demonstrated by the European Parliament's decision to increase the previous limit of 0.2% to 0.3% in October 2020.[23]

Within the UK, isolated CBD is not classified as a controlled substance, and only products that contain controlled cannabinoids, such as THC, are subjected to restrictions. The MHRA issued a statement indicating that cannabidiol products used for medical

TABLE 1 Examples of tetrahydrocannabinol (THC) limits for cannabidiol products in different countries

Country	THC limit/ %
France	0
Hong Kong	0
Argentina	0.2
Canada	0.3
Paraguay	0.5
Italy	0.6
Switzerland	1
New Zealand[21]	2

purposes were to be classed as medicines and would require authorisation before entering the market to guarantee consumer safety and product quality.[24] These regulations can therefore be avoided by suppliers by using alternative marketing strategies and avoiding making medical claims. Furthermore, the regulations enforced onto CBD edibles by the EU Novel Food Catalogue do not apply to CBD containing e-liquids.[25] Therefore, CBD e-liquids within the UK are instead regulated by the EU General Product Safety Directive 2001/95/EC. This means that there is no requirement for CBD quantities to be stated, leading to subjective descriptors such as 'CBD rich' on e-liquid packaging or no description at all.[26,27] This leaves consumers unaware of the dosage they will be receiving through usage of these products and cannot make judgement on appropriate consumption.

Similar legal outlooks are observed in different countries, where certain CBD-based products, such as oils fall under pharmaceutical regulations.[21] However, CBD-based e-liquids do not and therefore sit in a legal grey area.

6 | WHY ARE CANNABIDIOL LAWS IMPORTANT?

Members of the public are now actively seeking cannabidiol-enriched products for a number of reasons but particularly to help alleviate unwanted conditions such as chronic pain or anxiety. If the product chosen by an individual does not contain the labelled quantity of cannabidiol, the consumer will not receive the anticipated dosage, and this could limit drug efficacy, meaning they will not gain the therapeutic benefits they are pursuing.

The potential for drug-drug interactions between cannabidiol and common prescription medicines has been evaluated within the literature. Epidyolex, or Epidiolex, is a 100 mg/ml oral cannabidiol solution which has been medically approved for use to treat seizures associated with Lennox-Gastaut or Dravet syndrome.[28] The European Medical Agency indicates that strong inducers of the CYP isoforms 3A4 and 2C19 may cause a decrease in the bioavailability of CBD.[29] Examples of inducers include St. John's wort, rifampicin and carbamazepine.

Epidyolex also has a list of adverse reactions that have been noted from clinical trials which include insomnia, irritability, aggression, lethargy, diarrhoea and vomiting.[30] The most commonly occurring adverse effect was 'somnolence, sedation, lethargy and fatigue' with a combined frequency of 51% for a dosage 20 mg/kg/day.[30] A meta-analysis found there was a strong relationship between dosage of CBD and the likelihood of adverse events.[31] Whilst the typical strength of a CBD e-liquid ranges between 10 to 30 mg/ml, this may be sufficient to cause adverse effects and higher strength liquids are available claiming to contain up to 100 mg/ml.[26] Additionally, if the e-liquids do in fact contain more CBD than initially claimed, this also increases the risk of initiating adverse effects.

A survey of individuals using cannabidiol found that internet research was the most frequently reported method for learning about the cannabinoid.[32] This included those choosing to use cannabidiol to treat medical conditions and those purely seeking to improve their overall well-being. Individuals who decide to use cannabidiol e-liquids based off their own research without medical supervision may be unaware of possible interactions with any current meditation they are administering. This puts them at a higher risk of experiencing adverse reactions compared to those prescribed with approved CBD-based medication who will be adequately informed about drug interactions and monitored by professionals. Whilst CBD does not have the misuse potential in comparison to nicotine or THC, there are still risks associated with regular usage of CBD e-liquids.

7 | LABELLING ACCURACY IN CANNABIDIOL E-LIQUIDS

Seven articles have been published which determine the accuracy of labelling of cannabidiol content in e-liquids.[7,26,27,33–36] A brief summary of the findings of each experiment is provided in Table 2. These papers originate from three countries: one in Italy, two in Switzerland and four in America. In these papers, it was common practice to designate a ±10% variance from the labelled CBD content as an acceptable level of inaccuracy. Out of the 70 e-liquids tested in these articles that provided quantities for CBD concentration, 16 (22.9%) were considered to have accurate labels, 28 (40%) had overestimated and 26 (37.1%) had underestimated concentrations. Six e-liquids did not specify a CBD quantity on the packaging, and some were labelled with the descriptor 'CBD rich' and therefore were ruled out. These percentages are largely influenced by one group of authors who analysed 24 e-liquids and reported that 18 products had been mislabelled with underestimated CBD content.[7]

The range of these deviations is demonstrated using percentage differences in Table 3 and Figure 3. Each bar in Figure 3 represents both percentage increases and decreases within each of the defined intervals. This incorporates the results of 39 products as three of the papers did not provide sufficient data to allow for calculations. Several variations of units (mg, mg/ml and %) for quantifying CBD concentration were used across the articles considered. Wherever possible,

TABLE 2 Summary of the techniques used and results achieved in papers which analyse e-liquids

Ref.	Techniques used	Compounds detected	Brief summary of findings	Validation
Bonn-Miller et al.[7]	HPLC	CBD, CBDA, THC, THCA, CBN, CBG	Tested 24 e-liquids, 3 (12.5%) were accurate. 3 (12.5%) were below and 18 (75%) exceeded the labelled CBD content.	10-point method validation; LLOQ ≤ 0.3170% wt/wt; Limited information
Gurley et al.[26]	GC-FID, GC-MS	CBD, THC, 5F-MDMB-PICA, 5F-ADB	Tested 25 CBD products, 14 were e-liquids. 3 e-liquids contained synthetic cannabinoids. One e-liquid contained 45% THC. Two contained 5F-ABD, one contained 5F-MDMB-PICA	Modified from a previously published validated method; GC-FID LOD 0.12 μg/ml; GC-FID LOQ 0.35 μg/ml; Linearity up to 100 mg/ml; accuracy/precision ±15%. GC-MS (qualitative) validation not mentioned
Grafinger et al.[27]	FT-IR, GC-MS, UHPLC-DAD	CBD, CBDA, Δ^9-THC, Δ^8-THC, THCA, CBN, CBC, CBG, CBL, CBT, CBDV, CBEA	10 out of 20 samples were outside of the ±10% range, 8 were lower and 2 were higher than the label. THC was present in 18 samples but were all below 0.2%.	Validated 6-point calibration; R^2 > 0.9986; LLOQ 0.001 mg/ml; six QCs at 0.4% and 4% had precision ±20%RSD; 88–119% recovery; precision 0.27–6.86% RSD
Mazzetti et al.[33]	HPLC	CBD	Out of 13 samples, 5 e-liquids were within ±10% of labelled CBD amount. 5 were below labelled content and 3 were above.	Triplicate 5-point calibration R^2 0.995; standard addition method; Recovery 90–120%; LOD 1.70 μg/ml; LOQ 5.00 μg/ml; stability studies, e.g., −1.64 ± 0.22 mg/ml at 37°C
Peace et al.[34]	GC-MS, HPLC-MS/MS, DART-MS	CBD, THC, THCA-A, CBG, CBN, CBC	Labelled to contain 69% THC and 1% CBD. Analysed to contain 42.6% THC and 0.5% CBD.	Quantitative HPLC-MS/MS method modified from a previously published validated method; 7-point calibration 10–1,000 ng/ml
Peace et al.[35]	DART-MS, Headspace GC-FID, HPLC-MS/MS, SPME-GC/MS	CBD	Both e-liquids tested underestimated quantities, contained 230 and 197% of the labelled content.	Modified from a previously published validated method. Duplicate calibration 10–100 ng/ml with r2 0.9995; triplicate QCs at 10, 30, 300, and 750 ng/ml with ±15% accuracies
Giroud et al.[36]	GC-MS, HPLC-DAD, MSFTA derivatisation	CBD, THC, CBN, CBDA, CBGA, CBCA, CBVA.	Labelled as 2% CBD and 0.5% THC. Analysed content was 20% lower than the label.	Validation of HPLC-DAD quantitative method not mentioned; calibration 5 to 100 μg/ml

information provided within articles or from online retailers was used to convert all concentrations into mg/ml.

The majority of e-liquids (25, 61%) exhibited a percentage difference of between 0% and 20%. Eight e-liquids had a deviation of above 90%; the >100% difference came from an e-liquid labelled as containing 3.3 mg/ml which was found to contain 7.6 mg/ml.[35] Most notably, one e-liquid advertised to contain 1,000 mg of CBD was analysed and measured only 0.6 mg.[26] These results demonstrate how drastic the inconsistencies may be in the product labelling. However, these deviations may be in part due to product degradation over time from inadequate storage conditions. In one study,[33] thermostability and photostability studies were conducted. Thermostability studies consisted of performing experiments at 4°C, 22°C, and 37°C, for 30 days. Photostability studies were also conducted for 30 days by storing specimens in the dark and exposed to natural daylight. The loss CBD was measured statistically in both experiments, and the greatest reduction of CBD was seen at 37°C with average losses of CBD of 1.64 ± 0.22 mg/ml, which corresponded to 8/13 samples experiencing losses of above 10% of the initial concentration, and 5/13 samples, losses of between 5% and 10%. Following light exposure, losses of 1.83 ± 0.22 mg/ml were obtained.

To establish whether there was a statistically significant difference between the labelled and analysed CBD concentration,

TABLE 3 Information on the analysis of 39 CBD based e-liquids retrieved from four journal articles

Reference	Product name	Brand name	Labelled CBD/mg/ml	Analysed CBD/mg/ml	Percentage difference/%
33	Seven Wonders CBD 400	Vapoart	20	22.6	13
33	Seven Wonders CBD 200	Vapoart	10	8.9	11
33	CBD 200 Sativa Mr Kush	CBD Crystal	10	10.9	9
33	Ambrosia	Enecta	10	11.4	14
33	Mango Kush	Kanalife	20	18	10
33	CBD Liquid 1%	C-juice	10	0.8	92
33	CBD liquid 2.5%	C-juice	25	2.2	91
33	CBD liquid 5%	C-juice	50	4.0	92
33	CBD liquid 10%	C-juice	100	8	92
33	CBD pure 250	TNT vape	25	23.5	6
33	CBD 2%	Pure	20	20.8	4
33	CBD sativa blend	Sensi Seed	20	20.6	3
33	Pure Base	Harmony	30	35.1	17
25	Funky Farms Thin Mint	Arise Bioscience	350	417	19.1
25	Royal CBD Classic	Royal CBD	25	2	92
25	Exotic Watermelon Kush	Hempbombs	4.55	1.33	70.6
25	Silver Haze	VaporTech	8.33	4.47	46.4
25	Super Chill High Strength Cotton Candy	-	1000	0.6	99.94
25	Sweett Melons	Airbended Hemp	200	49	75.5
25	Diamond CBD	Diamond CBD	41.67	0.83	98
26	Strawberry Wild[a]	Harmony	10	10.05	0.5
26	Kiwi Skunk[a]	Harmony	10	8.81	11.9
26	Exodus Cheese[a]	Harmony	10	8.17	18.3
26	Moroccan Mint[a]	Harmony	10	8.89	11.1
26	New-York Diesel[a]	Harmony	10	9.28	7.2
26	Original Hemp[a]	Harmony	30	30.09	0.3
26	Freedom[a]	Cannaliz Terpenes+	30	27.87	7.1
26	Dreams[a]	Cannaliz Terpenes+	30	13.76	54.13
26	Mojito[a]	Cannaliz Terpenes+	30	22.96	23.47
26	Tangie[a]	Swiss E-liquid/Pure Production	10	8.99	10.1
26	Amnesia[a]	Swiss E-liquid/Pure Production	10	10.60	6
26	Critical[a]	Swiss E-liquid/Pure Production	10	11.79	17.9
26	Original Hemp	Marry jane	10	8.58	14.2
26	Original Hemp	Marry jane	30	33.46	11.53
26	Lemon[a]	Marry jane	10	9.99	0.10
26	Strawberry Wild	Marry jane	10	8.16	18.40
26	Melon[a]	Marry jane	10	9.53	4.70
35	Easy Rider	Cloud 9 Hemp	3.3	6.5	96.97
35	Yellow Brick Road	Cloud 9 Hemp	3.3	7.6	130.3

[a]E-liquids in which total THC content was determined, ranging from 0.0006% to 0.1059%.

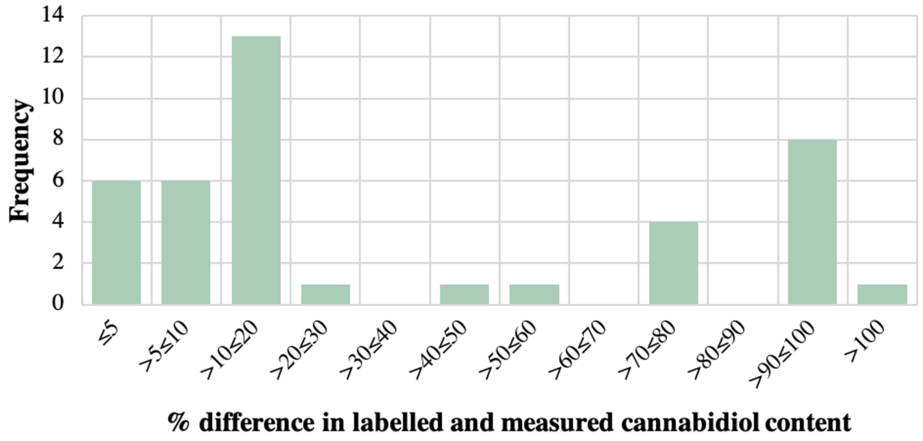
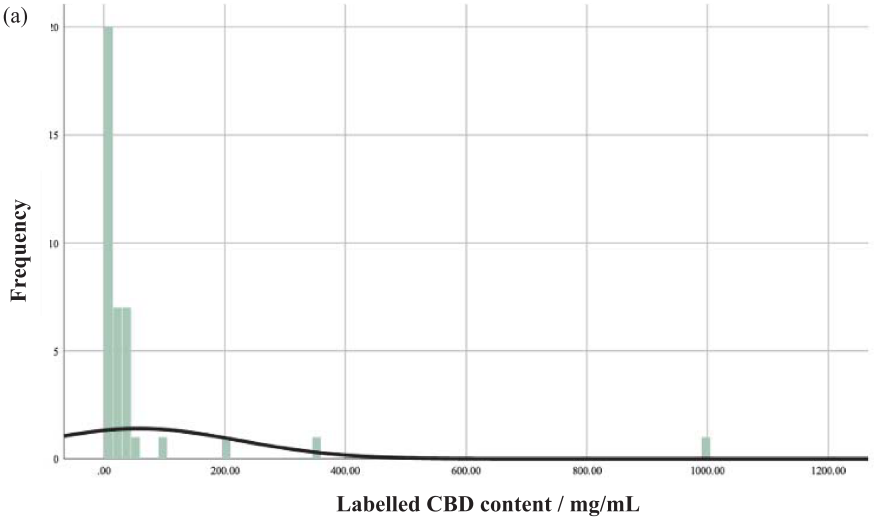
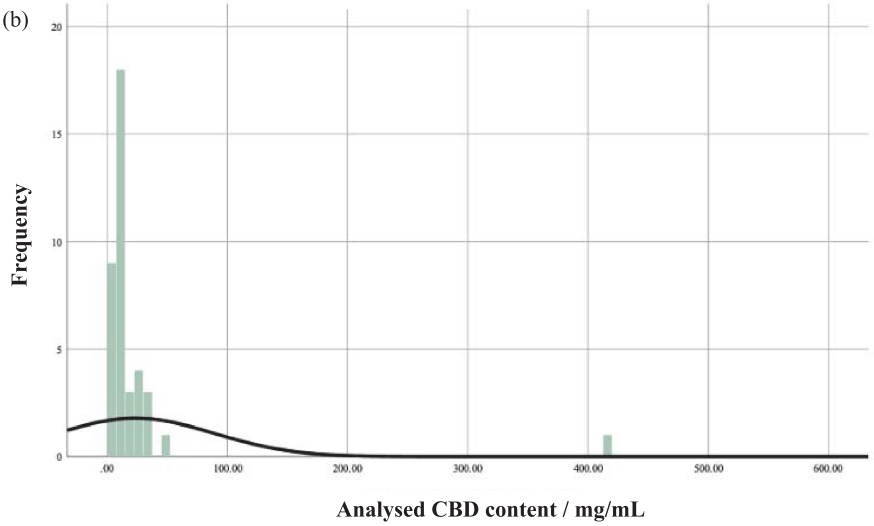


FIGURE 3 Percentage differences between advertised and analysed cannabidiol content in 39 CBD based e-liquids

(a)



(b)



(c)

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Labelled	.416	39	.000	.315	39	.000
Analysed	.379	39	.000	.269	39	.000

FIGURE 4 Histograms of (a) labelled and (b) analysed CBD concentrations in e-liquids to allow for visual analysis of distribution. (c) Results from the two conducted normality tests, Kolmogorov-Smirnov and Shapiro-Wilk, both indicating non-normal distributions ($p < 0.05$)

statistical analysis was performed. The distribution of both data sets was determined to aid in the decision of the most suitable statistical test. This was first achieved through graphical representation by plotting histograms with normally distributed curves superimposed (Figure 4). Further investigation was conducted through two normality tests, the Kolmogorov-Smirnov and Shapiro-Wilk tests. Both analyses indicated that the distributions were non-normal ($p < 0.05$). Therefore, a nonparametric test was the most appropriate choice. A previous study that explored significance by comparing the medians of advertised and measured CBD concentrations in commercial products used the Mann-Whitney U test.[37] In this case, both the Mann-Whitney U test ($p = 0.014$) and the Wilcoxon Signed Rank test ($p = 0.010$) provided sufficient evidence that the difference between the medians was statistically significant ($p < 0.05$).

8 | RATIONALE FOR FURTHER REGULATIONS

One of the reasons for regulation might be that the consumer is monitoring CBD use for medical reasons and therefore under labelling may have harmful consequences. From the viewpoint of a consumer's perspective (and also, e.g., that of the Federal Trade Commission in the USA), over labelling does not represent the product and can be considered fraudulent.

For regulatory reasons, measurement of CBD along with other cannabinoids assists in determining whether the CBD was added in its pure form or extracted from *C. sativa*, the latter being considered a DEA Schedule I drug unapproved for medical use by the FDA. An accurate representation of CBD is necessary to determine the likely origin of CBD.

In Switzerland, e-liquids are categorised as commodities that come into contact with the mucosal lining and cannot have constituents (including CBD) at pharmacologically relevant concentrations.[27] The CBD concentrations that can be added to e-liquids to satisfy this requirement are presently unclear. Therefore, a first step would be to monitor the concentrations that are being added. This, alongside schemes such as the Yellow Card scheme will therefore assist in garnering more information about the effects of CBD in such products so that the necessity of regulations for CBD concentrations, quality specifications and manufacturers' requirements, including labelling, could be ascertained.

Another major concern is that despite beneficial reported effects of CBD in a few studies which utilised regulated products such as Epidiolex®, these effects cannot be generalised and extrapolated to unregulated products. Furthermore, there is lack of clinical studies reporting the effects of use of chronic low-dose CBD, and therefore, CBD-containing e-liquids cannot be considered safe by default.[26]

A 10% deviation from label claims should be accepted based on the deviance allowed in USP product monographs for both manufactured products and compounded preparations.[33] This is further supported by other authors.[7,27]

9 | LIMITATIONS

The assessment of cannabidiol labelling inaccuracies in e-liquids is based upon the data published by other authors and relies on the assumption that this work is accurate. Only seven articles were identified that fit the eligibility criteria, and these originated from three different countries. It is possible that this set of articles does not give an accurate representation of the state of quality control in CBD-based vapes worldwide. However, each paper did report either the underestimated or overestimated quantities of CBD outside of the designated ±10% acceptable deviation.

10 | CONCLUSION

Whilst the directives and yellow card system put in place for nicotine-containing e-liquids in the UK ensure product quality, the grey area in which CBD containing e-liquids fall into means there are no enforced restrictions to guarantee their safety. There is currently no legal requirement for CBD concentration in an e-liquid to be stated on the product packaging. Inconsistencies in the labelling of CBD quantities have been identified, with 77.1% of e-liquids tested shown to have underestimated or overestimated the CBD quantity. Underestimations of CBD quantities may result in a larger risk of adverse reactions. Overestimations may mean that the e-liquids do not elicit the desired therapeutic effect. With the rapidly rising popularity of CBD e-liquids, it is essential that a method capable of regulating this industry is established and the introduction of regulations similar to the TPD may be a potential solution. More studies should be performed to determine the association between CBD concentration in the e-liquid and the inhaled dose.

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