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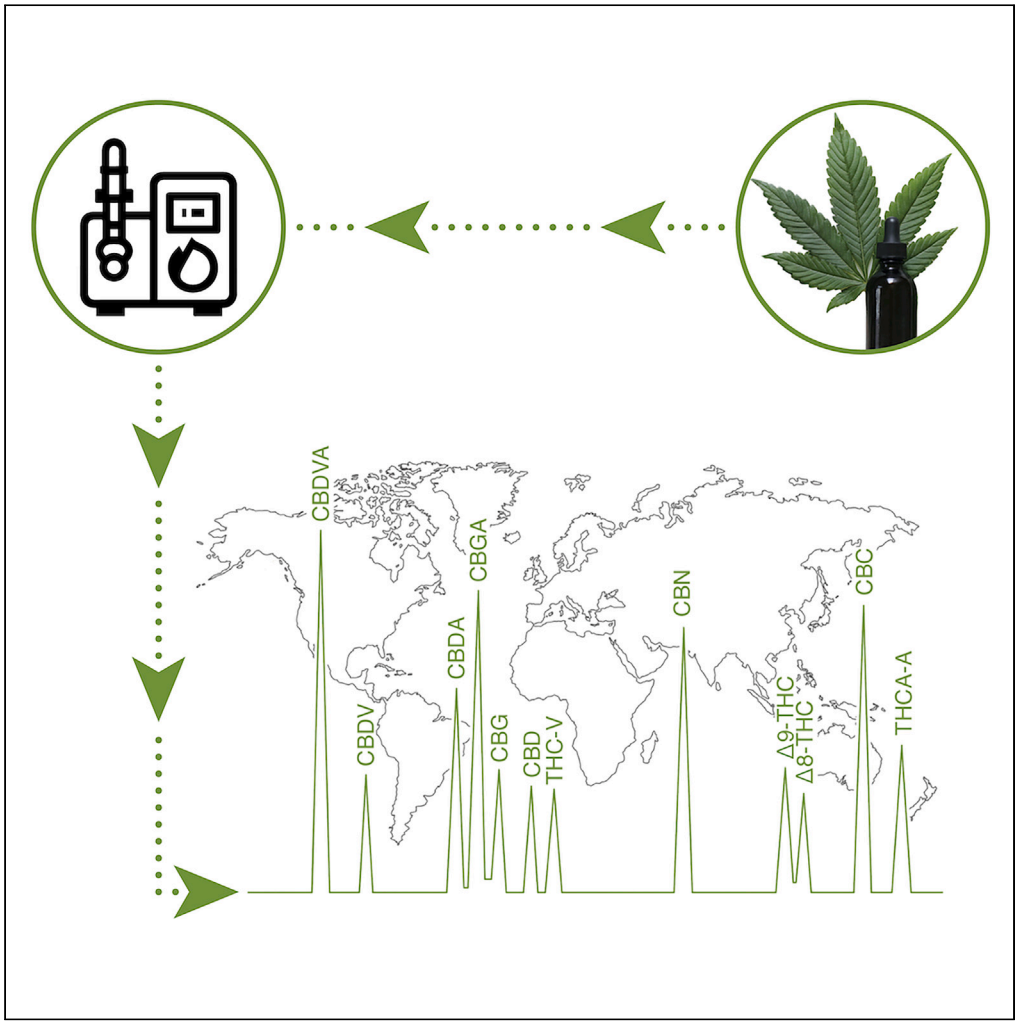

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Highlights

Cannabinoid (CBD) products have a broad range of concentrations of various cannabinoids

CBD concentrations declared on labels infrequently matched those of the e-liquids

Other cannabinoids, including Δ^9-THC, commonly found in CBD e-liquids

A number of approaches to minimize risk to consumers may be appropriate

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A multi-market comparison of composition, formulation, and label content of CBD e-liquids

Julia Hoeng,[1,6,*] Diogo A.R. S. Latino,[2] Walter K. Schlage,[3] Anatoly Mazurov,[1] Neil Sherwood,[4] Willie J. McKinney,[4] and Ian M. Fearon[5,*]

SUMMARY

The prevalence of electronically vaporized cannabidiol (CBD) use is rising in many countries. However, few regulatory frameworks exist for inhaled CBD, and this lack of oversight may not protect consumers from adverse consequences. We generated a representative map of several global consumer vaporized CBD markets by collating data concerning cannabinoid levels, including CBD and Δ^9-tetrahydrocannabinol, from the scientific literature. In addition, we analyzed several CBD e-liquids obtained in the UK. E-liquid CBD concentrations varied markedly both within and between markets. E-liquid CBD concentration commonly differed from the labeled amount, in one case by >200%, and fell outside a $\pm$10% tolerance. Other cannabinoids, including Δ^9-tetrahydrocannabinol, were commonly found in e-liquids. In summary, CBD e-liquids vary markedly in terms of CBD and other cannabinoid content, diluents, and contaminants. Due to the relatively unregulated state of the CBD vaporizer and e-liquid marketplace, consumers may be subject to harm associated with vaporized CBD use.

INTRODUCTION

Cannabidiol (CBD) is a member of the phytocannabinoid family of chemicals produced by the *Cannabis sativa* plant. While CBD is pharmacologically active and may have anti-inflammatory, analgesic, appetite-stimulant, anti-emetic properties[1,2] and is anti-convulsive in certain types of epilepsy,[3] CBD has not been found to be intoxicating, is not psychoactive, and presents no potential for abuse or dependence.[4–6] In addition, the use of CBD is well tolerated and not currently thought to be associated with significant adverse health risks.[7] The reasons for consumer (i.e., non-prescribed) use of CBD products have been extensively assessed, and while evidence for the efficacy of using CBD to self-manage medical conditions is sparse, reasons for consumer CBD use include the management of various mental and physical health symptoms,[8] and general well-being.[9] The global CBD consumer health market size was estimated at US$16 billion in 2022 and is expected to reach around US$62 billion by 2032.[10] This rapidly growing consumer demand for CBD is at least partly due to clinically unconfirmed beliefs that it may help manage specific medical conditions as well as to improve general well-being. In addition to growing consumer use, the increasing volume of scientific information on CBD has become challenging for both consumers and researchers as they strive to comprehend the real advantage and value of using CBD products from diverse sources.

In many countries around the world, inhaled CBD products can be lawfully marketed as consumer products, and in recent years the prevalence of use of electronically vaporized and other CBD products has risen.[11] The International Cannabis Policy Study assesses CBD use in all forms (including inhaled and oral use) in the United States (US) and Canada,[12] and in 2019 the prevalence of past 12-month CBD use was 16.2% and 26.1% in Canada and the US, respectively,[13] and a significant proportion of CBD use came from inhalational use. Among those reporting past 12-month use of CBD in any form, while the majority reported using CBD products less than once per month, a significant proportion (14.3% in Canada and 15.8% in the US) reported using CBD every day or almost every day.[13] This corresponds to a prevalence of daily/almost daily use of CBD products of approximately 2% in Canada and 4% in the US, and the vast majority of inhaled cannabis use in the US is in the form of use of vaporized e-liquids.[14] A similar prevalence of past 12-month use of CBD (18.5%) was reported for Switzerland in 2019,[15] and in the United Kingdom (UK) past 12-month use prevalence was estimated at between 8% and 11% of the population in that year, which equates to approximately 4–6 million UK adults.[11] In France in 2020, approximately 69% of adults had heard of CBD while one in ten had used it, with 1.6% of those who had used CBD using it daily or almost daily.[16]

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In some countries, the marketing of electronically vaporized products is subject to some degree of regulatory oversight. For example, in Switzerland, authorization to market a vaporized CBD product is required via a premarket submission to the Swiss Federal Office of Public Health containing information regarding tar and carbon monoxide content of the product, as well as a declaration that the product is not psychotropic. In addition, laboratory analyses are required to demonstrate that the product does not contain nicotine and contains Δ^9-tetrahydrocannabinol at a level no greater than 1%.[17] Similarly, in France the marketing of CBD products is lawful, and products must not contain Δ^9-tetrahydrocannabinol levels greater than 0.3%. In the UK, the Δ^9-tetrahydrocannabinol limit is set at 1 mg per container. In many other countries, however, the use of electronically heated CBD products is currently not subject to regulatory oversight. This includes the US, where the passing of the 2018 Farm Bill provided a legal justification for the manufacturing and sale of hemp-derived CBD products with less than 0.3% Δ^9-tetrahydrocannabinol.[18]

Many countries have adopted light regulatory oversight for electronically vaporized CBD products. Generally, these only include restrictions on psychoactive Δ^9-tetrahydrocannabinol content, and other aspects of CBD products such as the labeling of CBD content or product claims are unregulated and not currently subjected to regulatory approval. Vaporized CBD users are not aware of the current status of regulations and therefore might be exposed to potential risk. In addition, there is often little to no quality oversight, other perhaps than a routine duty of care burden placed on manufacturers. Such a lack of regulatory oversight can have deleterious consequences both for individual consumers and for public health.

Since the majority of CBD use, at least in the US, comes from the inhalation of vaporized e-liquids,[14] several studies have examined CBD e-liquid products which are marketed for vaporized CBD consumption. Largely, these studies have assessed the levels of both CBD and Δ^9-tetrahydrocannabinol in e-liquid products available to consumers and compared those contents to the product labels.[4,17,19–26] Generally speaking, these studies identified a range of CBD levels in these liquids, which deviated from the labeled contents and contained other cannabinoids such as Δ^9-tetrahydrocannabinol, often at psychoactive levels. CBD e-liquids also contained cannabinoids other than CBD or Δ^9-tetrahydrocannabinol and other potentially pharmacologically active compounds.

While CBD can be consumed in many different forms (e.g., inhaled, topical formulations, and edibles), the focus of this study was to assess CBD e-liquids intended for aerosolization and inhalation. We specifically aimed (1) to collate data from studies which assessed CBD e-liquids from the US, Swiss, UK, and European Union (EU) markets in order to assess the landscape of e-liquid CBD and Δ^9-tetrahydrocannabinol concentrations, (2) to assess the relationship between label CBD concentrations and the concentrations actually found in e-liquids, given that CBD e-liquid labeling is not currently subject to regulatory control, (3) to identify other chemicals found in CBD e-liquids, including other cannabinoids as well as diluents, and (4) to assess the utility of a market representative CBD e-liquid that could serve as a standard reference product in future toxicological investigations. We use the findings to highlight the need for reasonable regulatory oversight and standardization for the CBD e-liquid industry.

RESULTS

Data described in this paper were collated from the literature for the EU (Italy, Belgium, France, and Spain), Switzerland, and the US (including the states of New York and Mississippi as well as more widely available e-liquids and including both legal and illicit products) markets, while data for the UK market were also complemented with our own analytical chemistry assessments for 11 products.

E-liquid CBD concentrations

Data concerning CBD concentrations in all assessed e-liquids for each individual market are presented in Figure 1, with US data broken down into both legal and illicit products. Descriptive statistics are presented in Table S1. Median e-liquid CBD concentrations were 0.62% w/w for the EU e-liquids, 1.00% w/w for the Swiss e-liquids, 4.27% w/w for the UK e-liquids, 3.34% w/w for the lawful US e-liquids, and 1.18% w/w for the illicit US e-liquids. Interestingly, the CBD levels among the illicit US e-liquids were very tightly clustered around the median concentration compared with the liquids from other sources including the lawful US market, apart from a small number of outliers (Figure 1).

CBD e-liquid concentrations compared with labeled content

We also assessed e-liquid CBD concentrations as a function of the level reported on the individual product labels for products from the EU, Swiss, UK and US markets (Figure 2). Data were collated for 85 CBD e-liquids, either retrieved from scientific publications or analyzed by Triverity Laboratories, in which the CBD content of e-liquids was measured and compared with the claimed content on product labels. The majority of the data for the US market were retrieved from Gurley et al.,[20] who reported CBD content among 15 product samples that were obtained from commercial outlets in the US state of Mississippi.

For all countries/regions, the number of e-liquid CBD concentrations that fell within a $\pm$10% tolerance level of the label concentration was very low, ranging from 1 of 14 (7.1%) US e-liquids to 7 of 17 (41.2%) Swiss liquids. Overall, when combined across countries/regions, the proportion of e-liquids falling within the $\pm$10% tolerance level was 22.4%. Most commonly, and particularly for the EU and US e-liquids, the CBD concentrations were below the label-reported concentrations, and a number of these e-liquids contained very close to zero CBD when compared with the labeled content (Figure 2). The proportion of products below the tolerance level when compared to the labeled content ranged from 8 of 17 (47.1%) of Swiss e-liquids to 17 of 21 e-liquids (81.0%) in the UK, and it is notable in the UK that none of the e-liquids were above the labeled CBD concentration.

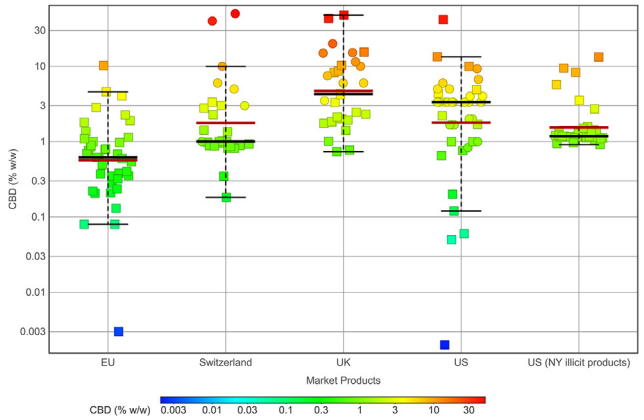

Figure 1. CBD concentrations in CBD e-liquid products from different markets

Data presented for the EU (n = 39), Swiss (n = 27), UK (n = 19), US legal (n = 42), and US illicit (n = 38) markets were collated from the literature or from label information. Data for the UK market (n = 11) were obtained from our own analytical chemistry assessments. Values are presented on a logarithmic scale with a color gradient according to the CBD concentration. Marker shapes: circles, data retrieved from label information of the products; squares, measured CBD concentrations retrieved from scientific publications (Table S1) or measured by Triverity Laboratories. Black bars indicate the median values, red bars indicate the mean values, the upper whisker indicates the greatest value smaller than 1.5 times the interquartile range above the third quartile, and the lower whisker indicates the smallest value greater than 1.5 times the interquartile range below the first quartile. Abbreviations: CBD, cannabidiol; EU, European Union; UK, United Kingdom; US, United States; NY, New York.

Among 24 UK samples, there was a tendency toward higher CBD labeled concentrations in disposable products (i.e., single-use products that cannot be refilled and are discarded once the battery or the liquid reservoir are depleted) when compared with products sold as refill e-liquids. While refill e-liquids had CBD concentrations ranging from 10 to 100 mg/mL (approximately 1%–10% w/w), the lowest and highest CBD concentrations in disposable products were 60 mg/mL (6% w/w) and 217 mg/mL (21.7% w/w), respectively (see Figure S1). For example, the disposable product D in Figure S1 indicated 20% CBD, while their refill solutions are available in 3% and 6% CBD (products H and I). Likewise, the disposable product C contained 7.5% CBD, and the corresponding refill e-liquid product O contained 3.5% CBD.

Δ^9-tetrahydrocannabinol concentrations in CBD e-liquids

Information concerning the Δ^9-tetrahydrocannabinol concentrations in 100 CBD e-liquids from the different markets is presented in Figure 3. Excluding the data from Duffy et al.,[24] who only assessed illicit CBD e-liquids in the US, overall Δ^9-tetrahydrocannabinol content in the various e-liquids was low and ranged from 0% to 1% w/w. To date, Δ^9-tetrahydrocannabinol has not been reported for any lawful US CBD e-liquids.

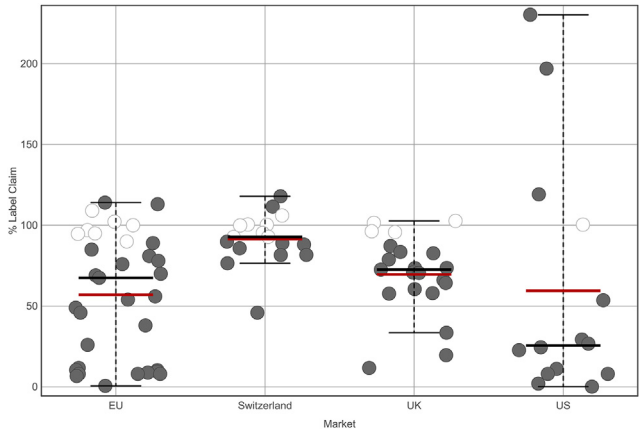

Figure 2. Percentage of analyzed CBD content relative to labeled CBD content of 85 e-liquid products from different markets

Data presented for the EU (n = 33), Swiss (n = 17), UK (n = 10), and US (n = 17) markets were collated from the literature or from label information. Data for the UK market (n = 11) were obtained from our own analytical chemistry assessments. White circles, CBD e-liquids with a percentage of labeled CBD content within a $\pm$10% tolerance. Gray circles, under-labeling (>110%) and over-labeling (<90%). Black bars indicate the median values, red bars indicate the mean values, the upper whisker indicates the greatest value smaller than 1.5 times the interquartile range above the third quartile, and the lower whisker indicates the smallest value greater than 1.5 times the interquartile range below the first quartile. Abbreviations: CBD, cannabidiol; EU, European Union; UK, United Kingdom; US, United States.

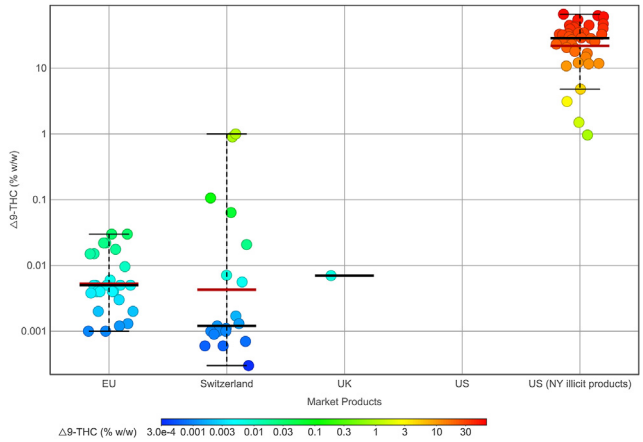

Figure 3. Δ^9-tetrahydrocannabinol concentrations in CBD e-liquid products from different markets

Data presented for the EU (n = 26), Swiss (n = 24), UK (n = 1), and US illicit (n = 38) markets were collated from the literature or from label information. No data were available for the legal US market. Data for the UK market (n = 11) were obtained from our own analytical chemistry assessments. Values are presented on a logarithmic scale with a color gradient according to the Δ^9-tetrahydrocannabinol concentration. Black bars indicate the median values, red bars indicate the mean values, the upper whisker indicates the greatest value smaller than 1.5 times the interquartile range above the third quartile, and the lower whisker indicates the smallest value greater than 1.5 times the interquartile range below the first quartile. No data are present in the literature regarding Δ^9-tetrahydrocannabinol levels in US CBD e-liquids other than for illicit products in the state of New York.[24] Abbreviations: Δ^9-THC, Δ^9-tetrahydrocannabinol; EU, European Union; UK, United Kingdom; US, United States; NY, New York.

However, Δ^9-tetrahydrocannabinol was found at high levels in illicit US e-liquids compared with other e-liquids,[24] with Δ^9-tetrahydrocannabinol concentrations ranging from 0.97% w/w to 66.3% w/w, and with median and mean values of 28.7% and 29.1%, respectively. Gurley et al.[20] only reported the detection of Δ^9-tetrahydrocannabinol at levels greater than 0.3% in 1 out of 15 CBD-containing e-liquid products analyzed. These data however are not shown in Figure 3 since actual analytical values were not reported in that study. Only 1 of the 11 UK e-liquids assessed by Triverity contained Δ^9-tetrahydrocannabinol, but at a fairly low level (Figure 3). A greater number of EU and Swiss e-liquids contained Δ^9-tetrahydrocannabinol at levels just above zero to 0.11% w/w. It has to be noted that all of the Swiss e-liquids contained Δ^9-tetrahydrocannabinol below the regulatory-mandated 1% maximum level.

Other cannabinoids found in CBD e-liquids

Data demonstrating the presence of cannabinoids other than CBD and Δ^9-tetrahydrocannabinol in US CBD e-liquids were collected from Duffy et al.[24] and also analyzed in UK e-liquids by Triverity Laboratories (Figure 4). Cannabichromene content information was retrieved for 38 e-liquids[24] and varied from 0.88% to 2.72% w/w. Cannabidiolic acid content information was retrieved for 38 out of 174 product samples, and this cannabinoid was not detected in 27 of 38 samples but was quantifiable in 11 of 38 samples. The cannabidiolic acid content in most of these 11 e-liquids was residual, ranging from 0.001% to 0.043% w/w, with the exception of two product samples with cannabidiolic acid contents of 0.23% and 5.45% w/w. The product containing a cannabidiolic acid concentration of 5.45% w/w was a "full spectrum" CBD e-liquid product from the UK with an advertised CBD content of 60%. Cannabidiolic acid was not detected in the remaining 10 UK products assessed by Triverity Laboratories.

Cannabidivarin content was retrieved only for two product samples from the label of the products with concentrations of 0.2% and 0.4% w/w. Cannabigerol content was retrieved for 50 out of 174 e-liquid samples. Cannabigerol was not detected in 4 of these 50 product samples (all samples were from the UK market and analyzed by Triverity Laboratories) and was below the limit of quantification (LOQ) in 18 of the 50 samples. Two products had relatively high cannabigerol concentrations of 7.7% and 6.5% w/w (data retrieved from label info), and both were advertised as CBD and cannabigerol blends.

Cannabinol content information was retrieved for 57 of the 174 e-liquids. Cannabinol was below the LOQ in 18 out of the 57 samples (18 out of 38 samples from New York state after the e-cigarette or vaping use-associated lung injury [EVALI] outbreak analyzed by Duffy et al.[24]) and was not detected in 10 of the 57 products samples (10 out of 11 samples from the UK market and analyzed by Triverity Laboratories). Cannabinol was quantifiable in only one sample from the UK market, in a product with a relatively high cannabinol content of 4.18% w/w. This product was advertised as a full-spectrum CBD product, and cannabinol content according to the certificate of analysis of the product was 0.528% w/w. In 8 product samples out of 20 analyzed from the Swiss market by Grafinger et al.,[17] the cannabinol content was residual and ranged from 0.008% to 0.024% w/w.

Tetrahydrocannabinolic acid content information was retrieved for 75 of the 174 product samples. Tetrahydrocannabinolic acid was not detected in 20 out of 20 e-liquid products analyzed by Barhdadi et al.[25] from the EU market nor in 11 out of 11 e-liquid product samples analyzed by Triverity Laboratories. Tetrahydrocannabinolic acid was quantified in residual amounts in 6 out of 20 e-liquids analyzed by Grafinger et al.[17] from the Swiss market. Tetrahydrocannabinolic acid was quantified in relatively higher concentrations by Duffy et al.[24] when

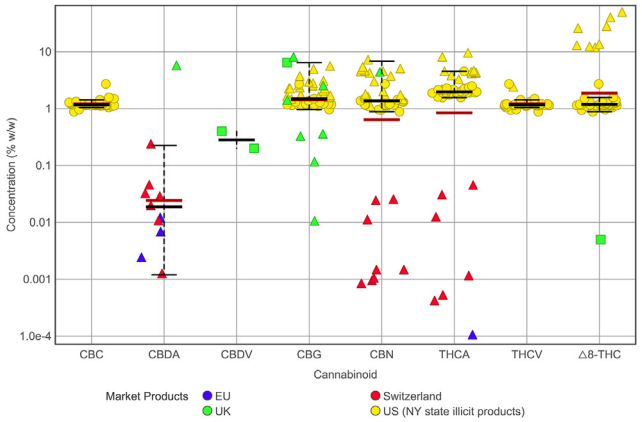

Figure 4. Concentrations of other cannabinoids in CBD e-liquid products from different markets

Data presented for the EU, Swiss, and US illicit markets were collated from the literature. No data were available for the legal US market. Data for the UK market were obtained from our own analytical chemistry assessments. No data were available for the legal US market. Data for the UK market were obtained from our own analytical chemistry assessments. For all cannabinoids assessed, each marker represents a single data point for that particular cannabinoid, and the color of each marker denotes the country/region from which the data were obtained. Values are presented on a logarithmic scale. Marker shapes: circles, represented values are below limit of quantification; squares, data retrieved from product label information; triangles, represented values are above the limit of quantification. Black bars indicate the median values, red bars indicate the mean values, the upper whisker indicates the greatest value smaller than 1.5 times the interquartile range above the third quartile, and the lower whisker indicates the smallest value greater than 1.5 times the interquartile range below the first quartile. Abbreviations: CBD, cannabidiol; CBC, cannabichromene; CBDA, cannabidiolic acid; CBDV, cannabidivarin; CBG, cannabigerol; CBN, cannabinol; THCA, tetrahydrocannabinolic acid; THCV, Δ-^{9}tetrahydrocannabivarin; Δ^{8}-THC, Δ^{8}-tetrahydrocannabinol; EU, European Union; UK, United Kingdom; US, United States; NY, New York.

compared with other markets and datasets. In that study, tetrahydrocannabinolic acid was quantified in 13 out of 38 e-liquids and ranged from 1.9% to 9.1% w/w.

Δ^{9}-tetrahydrocannabivarin content was retrieved for 49 of the 174 e-liquid samples. Δ^{9}-tetrahydrocannabivarin was detected in 11 of these 49 e-liquids (all samples were from the UK market and analyzed by Triverity Laboratories). For the remaining 38 product samples, Δ^{9}-tetrahydrocannabivarin was below the LOQ in 37 of them and was quantifiable in only one sample.

Δ^{8}-tetrahydrocannabinol content information was retrieved for 50 out of 174 e-liquids. Δ^{8}-tetrahydrocannabinol was not detected in 11 out of 50 e-liquids. These 11 product samples were from the UK market and were analyzed by Triverity Laboratories. Δ^{8}-tetrahydrocannabinol was below the LOQ in 30 out of 50 products and was quantifiable in only 8 out of 50 products (all of them illicit products from New York state analyzed by Duffy et al.[24]). In these 8 products, high levels of Δ^{8}-tetrahydrocannabinol were found, ranging from 11.3% to 47.1% w/w. In six samples, the concentration of Δ^{8}-tetrahydrocannabinol was higher than the concentration of Δ^{9}-tetrahydrocannabinol, and in one extreme case a Δ^{8}-tetrahydrocannabinol concentration of 47.1% w/w was found compared with a Δ^{9}-tetrahydrocannabinol concentration of 3.1% w/w.

Vehicles and other diluents in CBD e-liquids

Figure 5 presents a distribution plot showing the range of propylene glycol/vegetable glycerine (PG/VG) ratios of CBD liquids from all markets collated from the papers in Table S1, as well as the number of products containing vitamin E acetate and medium-chain triglycerides from Duffy et al.[24] The majority (31%) of e-liquids contained 50% PG/50% VG, though levels did range from 40% PG/60% VG (3 e-liquids) to 100% PG (2 e-liquids; Figure 5). Vitamin E acetate was detected in 23 of 38 (61%) CBD e-liquid samples analyzed by Duffy et al.,[24] with the concentration of vitamin E acetate determined to be in the range of 16%–57% w/w. From the same source, medium-chain triglycerides were detected in 14 of 38 (36.8%) samples with the concentration of medium-chain triglycerides ranging from 3% to 24% w/w.[24] The presence of vitamin E acetate and medium-chain triglycerides was mutually exclusive, in that vitamin E acetate and medium-chain triglycerides were not both found in the same e-liquids.[24]

DISCUSSION

The use of CBD e-liquids in vaporizer devices is becoming increasingly common, and the CBD market is growing rapidly. With this rapid growth comes a need to monitor the CBD marketplace to ensure that consumers are protected, not only in terms of health risks but also in terms of protecting consumers' rights under general consumer legislation. To more rigorously assess the CBD marketplace and fill knowledge gaps, particularly for the UK market, we used a two-pronged approach by collating information from the scientific literature and conducting analytical chemistry assessments. Overall, our findings demonstrate that marketed cannabinoid products have a broad range of concentrations of various cannabinoids, including the primary compound CBD, both within and between markets. The concentrations of CBD in these marketed products ranged from almost zero to over 40% w/w, although median levels between the different markets assessed fell inside a much smaller range. In addition, we also demonstrate that CBD concentrations declared on product labels infrequently matched

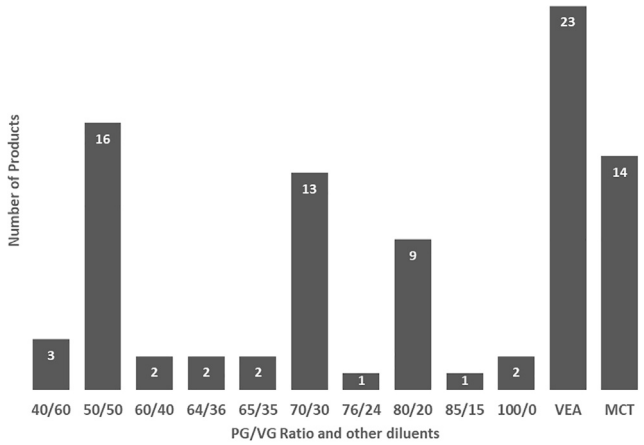

Figure 5. Distribution of products according to PG/VG ratio and other diluents

Data were collated from all markets (EU, Switzerland, UK, and US). Abbreviations: VEA, vitamin E acetate; MCT, medium-chain triglyceride oil; PG, propylene glycol; VG, vegetable glycerine; EU, European Union; UK, United Kingdom; US, United States; NY, New York.

those of the measured CBD concentrations. Interestingly, the actual CBD contents were commonly much lower than those claimed on product labels. Overall, while the sampling of CBD e-liquids for vaping assessed in this study was partly opportunistic and limited to only a few countries in which CBD products are sold, it is reasonable to conclude that there is a credibility gap regarding manufacturers' labeling of CBD concentrations, assessments of toxicity, and associated product claims or assurance of biological effects for the user.

While it may be that the cause for the large discrepancies between label CBD concentrations and those reported by analytical chemistry assays and the presence of other compounds in e-liquids for vaping reflect poor manufacturing standards, the presence of some contaminants could also result from degradation of CBD in vaping liquids over time.[4,19,27] Because CBD is polyphenolic in nature and vulnerable to oxidation and/or photodegradation, it may be unstable in marketed e-liquid compositions without appropriate formulation. CBD degrades in e-liquid solutions at ambient temperatures in dark and light[4,27] to form potentially undesirable products, including CBD, Δ^8-tetrahydrocannabinol, Δ^8-tetrahydrocannabinol cannabidibutol, cannabidihexol, cannabidiphorol, cannabidivarin, cannabidiol hydroxyquinone, cannabielsoin, hydroxy cannabidiol, and hydroxy-cannabielsoin.[27,28] Data in the literature suggest that at a storage temperature of 4°C, e-liquid CBD concentration can decrease by approximately 5% on average in 30 days.[4] At room temperature this decrease can become greater, up to approximately 20% on average at 37°C.[4] Furthermore, even after 1 day of storage at room temperature, CBD degradation products have been identified in e-liquids.[27] Differences were observed between different liquids, suggesting that characteristics of some e-liquids (e.g., other ingredients, pH) can affect CBD stability.[4] While reductions in CBD content may be of concern, rigorous toxicological risk assessments of the various degradation products are also required to minimize potential health impacts. An appropriate stability testing investigation starting with newly manufactured product could usefully address this issue.

Another noteworthy observation was the tendency toward higher CBD concentrations in the e-liquids of disposable products compared with e-liquids sold as refill solutions for re-usable devices as seen in the UK samples, which may need verification in a broader set of data including analysis of liquids from other markets. It remains unclear whether the disposable "pens" deliver the same amounts of CBD per puff as the re-usable devices deliver from the refill solutions, and whether different CBD transfer efficiencies in both systems might be responsible. More systematic research will be required to understand this phenomenon.

Δ^9-tetrahydrocannabinol, a psychoactive cannabinoid from the cannabis plant, has been identified in CBD e-liquids from various markets including the EU, Switzerland, the UK, and the US. In the European markets, our findings show that Δ^9-tetrahydrocannabinol levels were low, below the Swiss mandated limit for Δ^9-tetrahydrocannabinol in CBD e-liquids,[17] and in the UK its presence was rare, at least in the sample obtained from the UK market and subjected to our analytical assessment. In the US, Δ^9-tetrahydrocannabinol has been found in CBD e-liquids at high levels and is likely to have psychoactive effects as well as other potentially adverse effects in users,[29–31] although the levels seen were typically lower than those found in medical marijuana products.[24] It should be noted, however, that the e-liquids in which high levels of Δ^9-tetrahydrocannabinol were found were obtained from a specific US sub-market in the state of New York. Furthermore, these products were all illicit products and were vaporizer cartridges obtained from patients with EVALI during the outbreak of this condition in 2019.[24] Subsequent to the identification of the probable cause of EVALI, which was due to the inclusion of highly lipophilic solvents in illicit Δ^9-tetrahydrocannabinol and CBD e-liquids,[32,33] new cases ceased in mid-2020. However, whether high levels of Δ^9-tetrahydrocannabinol can still be found in CBD e-liquids has not been assessed.

In our study, using data both from Duffy et al.[24] and from our additional analytical assessments, cannabinoids other than CBD were found in a number of CBD e-liquids. This finding concurs with those of Guo et al.[21] following their assessment of cannabis e-liquid vaporizing liquids obtained from the market in California both before and after the EVALI outbreak in 2019. In that study, more than 100 terpenes and 19 cannabinoids were found in CBD e-liquids and derived vapors and aerosols.[21] In addition, and further in accordance with our findings, Guo et al.[21] also identified other additives, which are potentially harmful when inhaled, including vitamin E acetate and medium-chain triglycerides, in

cannabis e-liquids. Our analytical results also concur with the general picture drawn by other studies, which have identified various contaminants in CBD and cannabis e-liquids including cannabinoids other than CBD,[34–36] terpenes,[36,37] pesticides and fungicides,[24,36,38] potentially harmful solvents,[24,37–39] and Δ^9-tetrahydrocannabinol.[21,35–37] Potentially toxic metals, including copper, nickel, tin, and lead, likely arising from the contact between the e-liquid and the vaporizer heating coils, have also been identified in aerosols of vaporized nicotine and Δ^9-tetrahydrocannabinol e-liquids while copper was found in aerosol from a vaporized CBD e-liquid.[40] Furthermore, toxic aldehydes, including acetaldehyde, acrolein, crotonaldehyde, and formaldehyde, have been found in aerosol generated from nicotine, CBD, and Δ^9-tetrahydrocannabinol e-liquids, and these can be formed when heating PG, a solvent commonly found in e-liquids, at high temperatures. Overall, when taking into account our findings and those of others, large numbers of commercially available e-liquids and their aerosols contain varying contaminants, which have the potential to cause serious impacts on human health. This gives rise to a need for manufacturers to assess and control the levels of toxicants in CBD e-liquids and the vapor arising from their use.

The use of solvents and diluents identified in this study gives rise to a number of questions concerning both safety and consumer protection. The use of vitamin E acetate and medium-chain triglycerides is associated with the outbreak of EVALI in the US,[32,33] and both of these were found in a number of CBD e-liquids, particularly in illicit products. Their presence was however mutually exclusive, in that vitamin E acetate and medium-chain triglycerides were not both found in the same e-liquids. For PG and VG, the presence of these diluents in different proportions in nicotine-containing vapor products gives rise to differential aerosol generation and nicotine delivery.[41–44] By analogy, differing proportions of PG and VG in CBD e-liquids also give rise to differential delivery of CBD to users, and this may impact any desired biological effects. Further studies are required to understand the impact of the PG/VG ratio on CBD delivery to users of vaporized CBD e-liquids.

The findings of this study support a stepwise approach to addressing the shortcomings, and the potential for causing harm to consumers, of CBD e-liquids either currently or intended to be marketed to consumers. First, there is an immediate need to develop a reference CBD e-liquid representing the majority of marketed vaping products, possibly overseen by a standards development body, to create a consensus on appropriate content levels of e-liquid constituents and their vapor emissions. This reference product may then serve, in analogy to the standard reference cigarettes from the University of Kentucky,[45,46] as a probe in the development of analytical proficiency tests and, should preferred analytical method(s) eventually be selected, ring-trials to ensure continuous analytical competence. Although not aimed at commercialization, such a product may also serve as a helpful reference product with which to examine the uptake of vapor constituents among people who choose to use vaporized CBD e-liquids.

Second, a regulatory framework should be established to ensure that the presence of other cannabinoids, including Δ^9-tetrahydrocannabinol, in CBD e-liquids is kept within limits. This would minimize unwanted and unexpected consumer experiences as well as any associated toxicological risks. Additionally, such a regulatory framework should further mitigate any potential harms associated with vaporized CBD use by ensuring that chemicals such as pesticides are not found in CBD e-liquids. Lists of "banned ingredients," which are utilized in some countries for vaporized nicotine products, could be useful in this regard. For example, the 2014 revision of the EU Tobacco Products Directive, which has been implemented across the member states, put in place a regulatory framework, which bans the inclusion of certain ingredients (e.g., diacetyl) from nicotine e-liquids and places an onus on manufacturers to carry out testing to ensure levels of potential toxicants do not give rise to toxicological concern, and this has undoubtedly improved the quality and safety of vaporized nicotine products. Similar regulations for CBD products could protect consumers from adverse effects but should be put in place observing toxicological principles and following rigorous risk assessments to maximize CBD consumer protection while not placing an unnecessary burden on manufacturers.

Third, given that vapors generated from CBD e-liquids have been shown to contain metals and aldehydes,[40,47] the development of standardized devices and toxicant assessment techniques may also be warranted, as is the need for manufacturers to generate rigorous toxicological assessments of devices used for CBD vaporization, in order to mitigate the potential for risk in what is currently an unregulated consumer space with no mandated scientific standards in place. In this regard, it is notable that such standard devices and analytical laboratory techniques exist for nicotine-containing liquids and devices. For example, the US National Institute on Drug Abuse sponsored the development of a standard research electronic cigarette,[48,49] which was designed to produce a consistent, well-characterized aerosol for analytical testing, and the International Organization for Standardization[50] and the Cooperation Center for Scientific Research Relative to Tobacco,[51] among other organizations, have issued recommended testing methods for the machine generation of e-cigarette aerosol. Additionally, the French standards organization Association Française de Normalisation published in 2016 a standard method for characterizing e-cigarette emissions and, in doing so, also set emissions target levels for acrolein, acetaldehyde, formaldehyde, antimony, nickel, chromium, cadmium, lead, and arsenic. Applying similar standard setting approaches to CBD products, along with regulatory-mandated use of standards and routine product testing, may be of importance for consumer CBD products to minimize risks of harm to consumers. In making this recommendation, however, we are conscious of data gaps in the CBD literature. For example, there are no studies which have assessed puffing topography of vaporized CBD users, and the informed setting of machine parameters for standardized puffing would require such data since it likely differs from e-cigarette puffing topography. This is particularly pertinent given that standardized regimens for machine collection of aerosol from nicotine-containing e-cigarettes may not necessarily reflect actual use patterns and behaviors.[52] Further studies would therefore be required to assess CBD user puffing topography in order to inform any standards setting process.

Limitations of the study

The work we present in this manuscript should be placed into context with some limitations. We have generated a comprehensive market map of CBD e-liquids across several countries and regions and described the presence of varying levels of CBD, Δ^9–tetrahydrocannabinol, other cannabinoids, and diluents. However, the vaporized CBD marketplace is large, growing, and dynamic. Our findings are therefore

limited to what data were available in the existing literature on products which were marketed at the time at which those studies were conducted, and also to data from a number of CBD e-liquids available in the UK market at the point in time at which we conducted our own additional analyses. As the CBD e-liquid marketplace is constantly changing, our market map may not reflect current or future e-liquids as different products enter, or are removed from, markets around the world. Our findings are also limited to e-liquid composition, and few studies have assessed the aerosol from CBD vapor products.[53] Future studies are required to build on the evidence we present, to assess transfer and the presence and levels of potential contaminants in vaporized CBD aerosols, and to perform toxicological risk assessments using data from such studies.[54] Taking such an approach will undoubtedly help to protect consumers from adverse health consequences by informing evidence-based regulation of CBD e-liquid products.

In summary, from our analyses of data from both the existing literature and our own analytical assessments, we have demonstrated that CBD e-liquids intended for use in electronic vaporizers vary markedly in terms of CBD content, diluents, the presence of other cannabinoids including Δ^9-tetrahydrocannabinol, terpenes, and also the presence of contaminants such as pesticides and carbonyls. Due to the current, relatively unregulated state of the CBD vaporizer and e-liquid marketplace, consumers may be subject to risk of harms associated with vaporized CBD use. Well-characterized CBD liquids for vaping will be essential to meet emerging regulatory demands for safety and satisfy consumer expectations in this rapidly growing market. However, a number of approaches to minimize potential product-induced health risk to consumers may be appropriate, including establishing regulatory approaches to oversee products before they are introduced into the market. This may include standards for development and testing of devices and e-liquids, maximum vapor constituent levels, and manufacturing quality.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Dr. Julia Hoeng (julia.hoeng@vecturafertinpharma.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Data: all data reported in this paper will be shared by the lead contact upon request.
- Code: this paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

D.A.R.S.L., W.K.S., and A.M. analyzed the data and generated the tables and figures. I.M.F., N.S., W.J.M., D.A.R.S.L., W.K.S., A.M., and J.H. wrote the manuscript.

DECLARATION OF INTERESTS

J.H. is the Chief Innovation Officer of Vectura Fertin Pharma, a manufacturer of wellness and healthcare products, including CBD products. D.A.R.S.L. is a lead consultant in chemistry at Rosa Serra Latino Consulting. W.K.S. is a freelance consultant in biology paid by Vectura Fertin Pharma. I.M.F. is the Director of whatIF? Consulting Ltd, a company which provides scientific and regulatory support to tobacco and nicotine product manufacturers, and to contract research organizations. I.M.F. is a Scientific Advisory Board member of Qnovia, Inc, and holds stock in the company. I.M.F. is also a Non-Executive Director of Advanced Inhalation Rituals Ltd. A.M. is a medicinal chemistry consultant at Philip Morris Products S.A. N.S. works as an independent consultant advising on regulatory science for conventional and new-generation tobacco and nicotine and CBD products. W.J.M. is the Founder and CEO of McKinney Regulatory Science Advisors, LLC, a services company which provides scientific and regulatory guidance to nicotine and cannabis product manufacturers.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
Cannabichromene standard 1000 μg/ml in methanol	Restek Thames, Saunderton, UK	34092
Cannabichromene standard 1 mg/ml in methanol	Cerilliant, Round Rock, Texas, USA	C-143
Cannabidiol standard 1000 μg/ml in methanol	Restek Thames, Saunderton, UK	34011
Cannabidiol standard 1 mg/ml in methanol	Cerilliant, Round Rock, Texas, USA	C-045
Cannabidiolic acid standard 1000 μg/ml in acetonitrile	Restek Thames, Saunderton, UK	34094
Cannabidiolic acid standard 1 mg/ml in acetonitrile	Cerilliant, Round Rock, Texas, USA	C-144
Cannabidivarin standard 1000 μg/ml in methanol	Restek Thames, Saunderton, UK	34123
Cannabidivarin standard 1 mg/ml in methanol	Cerilliant, Round Rock, Texas, USA	C-140
Cannabidivarinic acid standard 1000 μg/ml in acetonitrile	Restek Thames, Saunderton, UK	34134
Cannabidivarinic acid standard 1 mg/ml in acetonitrile	Cerilliant, Round Rock, Texas, USA	C-152
Cannabigerol standard 1000 μg/ml in methanol	Restek Thames, Saunderton, UK	34091
Cannabigerol standard 1 mg/ml in methanol	Cerilliant, Round Rock, Texas, USA	C-141
Cannabigerolic acid standard 1000 μg/ml in acetonitrile	Restek Thames, Saunderton, UK	34135
Cannabigerolic acid standard 1 mg/ml in acetonitrile	Cerilliant, Round Rock, Texas, USA	C-142
Cannabinol standard 1000 μg/ml in methanol	Restek Thames, Saunderton, UK	34010
Cannabinol standard 1 mg/ml in methanol	Cerilliant, Round Rock, Texas, USA	C-046
Δ^8-tetrahydrocannabinol standard 1000 μg/ml in methanol	Restek Thames, Saunderton, UK	34090
Δ^8-tetrahydrocannabinol standard 1 mg/ml in methanol	Cerilliant, Round Rock, Texas, USA	T-032
Δ^9-tetrahydrocannabinol standard 1000 μg/ml in methanol	Restek Thames, Saunderton, UK	34067
Δ^9-tetrahydrocannabinol standard 1 mg/ml in methanol	Cerilliant, Round Rock, Texas, USA	T-005
Tetrahydrocannabivarin standard 1000 μg/ml in methanol	Restek Thames, Saunderton, UK	34100
Tetrahydrocannabivarin standard 1 mg/ml in methanol	Cerilliant, Round Rock, Texas, USA	T-094
Δ^9-tetrahydrocannabinolic acid standard 1000 μg/ml in acetonitrile	Restek Thames, Saunderton, UK	34111
Δ^9-tetrahydrocannabinolic acid standard 1 mg/ml in acetonitrile	Cerilliant, Round Rock, Texas, USA	T-093

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

No experimental models were used in the study, and the study did not involve human participants.

METHOD DETAILS

Literature search strategy and data sources

In order to collect data concerning the concentrations of cannabinoids and other ingredients (e.g., flavors, diluents) reported from studies of e-liquids used for CBD aerosolization in a representative sample of markets in the EU (Italy, Belgium, France, and Spain), Switzerland and the US (including the states of New York, Mississippi as well as more widely-available e-liquids), quantitative analytical data and declared product data were obtained through searches of scientific literature databases and by collating information from websites of manufacturers and distributors. In addition, due to the paucity of reported data on UK CBD products, we conducted a dedicated analysis of products purchased on the UK market (Figure S2).

Internet literature searches were conducted manually using reference lists of original papers and review articles, resulting in eleven original papers reporting quantitative analytical data on e-liquids containing CBD, obtained by various analytical methods; those articles providing quantitative analytical results for individual e-vape products are summarized in Table S2. For a general estimation of non-cannabinoid ingredients, e.g., diluents and terpenes, summary data and qualitative data from additional publications were also considered.

To complement the collection of data sources, a broader systematic PubMed search covering the time period from January 2018 to July 2023 was conducted by EDANZ (https://www.edanz.com), using the following MESH terms, keywords, and search string.

(1) *MESH terms:* Vaping, cannabinoids, cannabinol, dronabinol
(2) *Keywords:* Cannabidiol, cannabidiolic acid, cannabidivarin, cannabigerol, cannabinoid*, cannabinol, CBD, CBDA, CBDV, CBG, CBN, d8-tetrahydrocannabivarin, d8-THC, d9-THC, delta-8-tetrahydrocannabinol, E-Cig, ecigarette, e-cigarette, electronic cigarette, e-liquid*, tetrahydrocannabinol, tetrahydrocannabinolic acid, tetrahydrocannabivarin, THCA, THCV, vape, vaping
(3) *Search String:* ("Vape"[Text Word] OR "Vaping"[Text Word] OR "E-Liquid*"[Text Word] OR "E-Cig*"[Text Word] OR "ECig*"[Text Word] OR "Electronic Cig*"[Text Word]) AND ("Cannabinoid*"[Text Word] OR "Cannabi*"[Text Word] OR "Tetrahydrocanna*"[Text Word] OR "CBD"[Text Word] OR "CBG"[Text Word] OR "CBN"[Text Word] OR "THC"[Text Word] OR "CBDA"[Text Word] OR "CBDV"[Text Word] OR "THCV"[Text Word] OR "THCA"[Text Word])

This resulted in a raw list of 589 articles, which were further screened and manually searched for eligible content using the title and the abstract, particularly to contain quantitative e-liquid information on CBD and other cannabinoid concentrations, yielding a total of 12 filtered articles (Figure 1) that included eight articles from the initial manual search.

For our numerical evaluations of the CBD and THC content, repetitive data from review articles were excluded, as were articles that reported analytical data of other constituents but not CBD concentrations. Declared cannabinoid concentrations were obtained primarily from the publications comparing analyzed and declared concentrations of CBD and, if available, also of diluents and other selected ingredients in CBD e-liquid products from the US, Swiss, UK, and EU markets. Additional declared CBD and Δ^9-tetrahydrocannabidiol concentrations, particularly for products in the US, Swiss and UK markets, were obtained for arbitrarily selected brands from various distributors' and manufacturers' websites (Table S3).

Analytical chemistry

Analytical methods used in the nine selected referenced articles described above, are summarized in Table S2.

For the UK market, few specific analytical data for e-liquids were available. Therefore, a limited market sample of 11 e-liquid products was purchased and analyzed for the concentrations of a number of cannabinoids (CBD, cannabichromene, cannabidiolic acid, cannabigerol, Δ^9-tetrahydrocannabivarin, cannabidivarin, cannabinol, Δ^9-tetrahydrocannabinol, Δ^8-tetrahydrocannabinol, and tetrahydrocannabinolic acid) by Triverity Laboratories (Newtownabbey, County Antrim, UK). The 11 products were selected as the market-leading CBD e-liquids available in the UK market and are thought therefore to be representative of the UK market at the time at which the analyses were conducted (January to March 2023).

Two methods were used by Triverity Labs to assess cannabinoid content of the selected e-liquids; (1) for normal cannabinoid levels (30–70 μg/mL) and (2) for low level cannabinoids (LLC; 0.01–1.6% w/w). Both methods are applicable to the analysis of oil- and oil/solvent-based liquids, and utilised reverse phase ultra-performance liquid chromatography (UPLC) with a formic acid/acetonitrile gradient using a C18 column and methanol as the diluent. Test samples were diluted to match the indicated concentration ranges (normal or LLC), based on the labeled contents of the products. Analytical reference standards used are listed in the key resources table. Reference standards A and B for CBD and cannabigerol were prepared to contain 50 μg/mL and 30 μg/mL for the normal range method, and 1 μg/mL and 6 μg/mL for the LLC method. Reference standards for the LOQ were prepared to contain 0.1 μg/mL. For the identification of peaks of the other cannabinoids, a composite reference standard containing cannabidiolic acid, cannabidivarin, cannabidivarinic acid, cannabigerolic acid, tetrahydrocannabivarin, cannabinol, Δ^9-tetrahydrocannabinol, Δ^8-tetrahydrocannabinol, Δ^9-tetrahydrocannabinolic acid and cannabichromene was prepared. Peaks present were required to be greater than the LOQ to ensure identification certainty.

A UPLC 1290 (Agilent Scientific Instruments, Didcot, UK) with quaternary pump and diode array detector was used with the following parameter settings: Supelco Ascentis Express C18, 2.0 μm, 150 × 2.1 mm column; 25°C column temperature; 10°C sample tray temperature; run time of 11 min for CBD or cannabigerol, and 17 min for LCL); mobile phase A 0.01% formic acid in water; mobile phase B acetonitrile; injection volume 2 μL for CBD or cannabigerol and 1.1 μL for LLC; detection 240 nm with 10 nm bandwidth; ref. 360 nm with 50 nm bandwidth; peak width >0.025 min; and slit 4 nm.

Following the usual calculations of noise, standard concentrations, recovery rates, drift checks, and LOQ, the concentration of CBD was calculated from data obtained by the normal range method:

$$\text{Concentration } (\%w/w) = \frac{A_{Samp}}{A_{StdA}} \times C_{StdA} \times \frac{\frac{DF}{M}}{1000\mu g} \Big/ \text{mg} \times 100$$

Where M = weight of the sample (mg), $C_{Std\ A}$ = concentration of standard A (μg/mL), DF = dilution factor if applicable (example: 25/5), A_{Samp} = area of the sample, and $A_{Std\ A}$ = mean area of Standard A.

The concentrations of the other cannabinoids present in minor amounts were calculated from data obtained by the LLC method:

$$\text{Concentration } (\%w/w) = \frac{A_{Samp}}{A_{LLC-A}} \times C_{LLC-A} \times \frac{1000mL}{M} \times \frac{1mg}{1000\mu g} \times RRF \times 100$$

Where A_{Samp} = area of the sample, $A_{LLC\text{-}A}$ = mean area of LLC-A, $C_{LLC\text{-}A}$ = concentration of LLC-A (μg/mL), RRF = relative response factor, and M = sample weight in mg.

QUANTIFICATION AND STATISTICAL ANALYSIS

The primary focus of this investigation was on the CBD content (and if available, also Δ^9-tetrahydrocannabidiol content) of the CBD-containing e-liquids. The reported analytical and label values are presented separately for the USA, UK, EU, and Switzerland. In each figure, individual data points are presented graphically along with descriptive statistics including means, medians, and interquartile ranges.