International Journal of Drug Policy 124 (2024) 104313

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

Research Paper

Reported exposures to derived cannabis products in California before and after the 2018 federal reclassification of hemp

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ARTICLE INFO

Keywords:
Marijuana
Cannabinoids
Child
Poisons

ABSTRACT

Background: As of June 2023, a majority of states had legalized the sale of cannabis, which past research has found to be associated with increased exposures. In 2018, a change in federal policy increased access to cannabidiol (CBD) and derived psychoactive cannabis products, but there has been limited study of reported exposures following this change.

Methods: This observational retrospective study analyzed exposures involving synthetic cannabinoid receptor agonists (SCRAs) and derived cannabis products, including CBD, reported to the California Poison Control System (CPCS) from 2010 to 2022. We focused primarily on potential shifts in reported exposures before and after the implementation of the 2018 Farm Bill, which removed products derived from hemp from the Controlled Substances Act. We reviewed and hand-coded individual call records to assess reported exposures over time and their characteristics, and conducted interrupted time series analysis to assess whether exposure counts changed after policy interventions.

Results: Reported CBD exposures significantly increased following the federal reclassification of hemp products. Exposure reports were most common among young children and for edibles. Exposure reports provided limited information about derived psychoactive cannabis products.

Conclusions: Our findings suggest a need for improved data collection regarding derived psychoactive cannabis products, as well as potential public health value in modifying packaging regulations and in providing additional guidance to parents to help prevent CBD exposures.

Introduction

In the 21st century, attitudes and laws in the US relating to traditional cannabis relaxed substantially; as of mid-2023, 38 states, 3 territories, and the District of Columbia had legalized medical use of cannabis products, and 23 states and the District of Columbia had legalized recreational use (National Conference of State Legislatures 2023). These regulatory changes have been associated with increases in cannabis use, as well as misuse and associated health harms (National Institute on Drug Abuse 2019). In addition, at the federal level, the 2018 Farm Bill, implemented in January 2019, removed hemp and its derivatives from the Controlled Substances Act as long as they contained no more than 0.3% delta-9 tetrahydrocannabinol (delta-9 THC) by dry weight (National Institute of Food & Agriculture 2023). Although the US Drug Enforcement Administration issued a notice of intent in April 2023 to regulate some hemp derived cannabis products, the effects of this notice remained unclear at the end of 2023 (US Food & Drug Administration 2023).

Cannabidiol (CBD), a non-psychoactive derived cannabis product, has been extensively marketed after the federal reclassification of hemp products (Amin & Ali, 2019). There is little oversight of CBD products with respect to purity or content, as a result, there have been reports of CBD gummies formulated with other ingredients such as melatonin and sold as dietary supplements (Berger et al., 2021; Cohen et al., 2023; Walker et al., 2020). There have also been anecdotal and popular media reports that the use of derived psychoactive cannabis products such as delta-8, delta-10, and HHC, (Rossheim et al., 2023) commonly referred to "synthetic" weed, pot, or cannabis in the popular media and trade press, increased in the US after the passage of the 2018 Farm Bill (Casacchia, 2023; Geci et al., 2023; Kary, 2023; Mark et al., 2020; U. S.

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https://doi.org/10.1016/j.drugpo.2023.104313

Available online 8 January 2024

Food & Drug Administration 2022). These products have high levels of THC analogs and users report they have similar psychoactive effects to delta-9 THC yet make it possible to pass urine drug screens (Geci et al., 2023; Kelly & Nappe, 2023). Historically, the term "synthetic cannabis" was used for products marketed using names such as "Spice," "K2," and "incense" that became available in the US in 2008 and were later banned by multiple states due to their toxicity and potential for abuse, especially among young people (America's Poison Centers 2023; Brents & Prather, 2014; Law et al., 2015; Malaca et al., 2022; Mills et al., 2015; Tait et al., 2016; Zaurova et al., 2016). Health researchers term these products synthetic cannabinoid receptor agonists (SCRAs); America's Poison Centers reported that SCRA exposures declined substantially by 2019, an outcome likely associated with federal and state regulation intended to deter use (Klein et al., 2022).

There is an extensive literature documenting traditional cannabis and SCRA exposures reported to poison centers, which have found increasing unintentional exposures to traditional cannabis among children (Forrester, 2012; Forrester et al., 2012; Graves et al., 2023; Laudone et al., 2022; Leubitz et al., 2021; Roth et al., 2022; Sznitman et al., 2020; Tweet et al., 2023). Efforts to identify shifts in derived psychoactive cannabis product exposures have been hampered by terminology: popular media reports frequently refer to "synthetic cannabis" without distinguishing whether they mean SCRAs or derived psychoactive cannabis products, as do users. We identified one prior study of CBD exposures in the research literature showing increased exposures in the US from 2014 to 2021 (Perez-Vilar et al., 2023), but little research attempting to distinguish between SCRAs and derived psychoactive cannabis products.

Understanding the extent and nature of exposures related to novel derived cannabis products is critical to determining the extent to which exposures have increased and whether interventions may be warranted. In this study, we assessed exposures to CBD, derived psychoactive cannabis products, and SCRAs reported to the California Poison Control System (CPCS) from 2010 to 2022. Given that prior research has reported disproportionate traditional cannabis exposures among young people, and among males for SCRAs, we reviewed whether patterns were similar for derived cannabis products. We assessed exposures for both derived psychoactive cannabis products and SCRAs given that the term "synthetic cannabis" has been widely used for both. We focused our research on California; California by itself constitutes the world's largest legal cannabis market (State of California Department of Justice 2022; Why California is the World's Largest Cannabis Market 2018), and as a result, residents can purchase traditional cannabis, CBD, and derived psychoactive cannabis products from retailers. Our use of state-level poison control records allowed us to review individual chart notes, which was critical to distinguishing between different product types. We anticipated that exposure reports for derived psychoactive cannabis products and CBD would increase following implementation of the 2018 Farm Bill.

Methods

Study design

This observational retrospective study analyzed trends in CBD, derived psychoactive cannabis product, and SCRA exposures reported to the CPCS from 2010-2022. Our primary focus was on possible changes in exposures after the implementation of the 2018 Farm Bill in January 2019, which legalized products derived from hemp with less than 0.3% delta-9 THC (traditional cannabis). As secondary objectives, we considered changes in SCRA exposures after the Synthetic Drug Abuse Prevention Act of July 2012 and the September 2016 California SCRA ban, which took effect in January of 2017.

Data source and collection

The CPCS database was searched for exposure cases involving CBD, derived psychoactive cannabis products, and SCRAs from January 1, 2010, to December 31, 2022. We first identified cases by searching product and generic NPDS codes for cannabidiol, synthetic cannabinoids, and marijuana. Additional freetext/keyword searches of the verbatim substance field and history field were performed to identify additional records. These keywords were terms used in popular media and research literature to refer to SCRAs (e.g., spice) and derived cannabis products (e.g., delta, CBD, cannabidiol). Details of the search strategy, including NPDS codes, are provided in the Supplement. Both free-text and product/generic code searches were needed for case identification because specific codes for these substances did not exist throughout the entire study period. In addition, at the time of the search, there was no specific code identifying derived psychoactive cannabis products such as delta-8. Each case was counted once using a CPCS identifier, even though a record could be identified through both a free-text and generic product code search. We excluded calls originating outside of California, animal exposures, and calls for information that did not involve a reported toxic exposure to a relevant product. The University of California San Francisco (UCSF) Institutional Review Board approved this research on December 9, 2022 (#20-32966).

Measures

We defined an exposure as actual or suspected contact with any substance that had been ingested, inhaled, absorbed, applied to, or injected in the body, regardless of toxicity or clinical manifestation. Call records were individually read by an investigator to determine that exposures involved CBD, SCRAs, or derived psychoactive cannabis products, to check whether exposures involved a single substance or multiple substances, and where possible, to detail the nature of the product involved in each exposure, specifically product type, and if included in the call record, product name. Measures coded automatically by CPCS and contained in the call record database included the date of the call, age of the person exposed, self-reported gender, and route of exposure (e.g., inhalation, ingestion).

Record coding

Each call record was individually read and hand-coded by investigators using REDCap (Research Electronic Data Capture), a secure and HIPAA-compliant web-based system to support research studies (Harris et al., 2009; Harris et al., 2019). We first drew a random sample of 200 CPCS call records; each of these records was double-coded by two of three authors (KM, RFC, and SS) to determine whether it met inclusion criteria and if so, the product type. Each of the investigators involved in coding records was a PharmD student that had completed two years of training. We used Gwet's AC1 to calculate interrater reliability (Gwet, 2014) for three primary measures: exposure met inclusion criteria (yes or no), substance type (CBD, SCRA, or derived psychoactive cannabis product), and exposure to single versus multiple substances. Outcomes for these three measures were 0.85, 0.92, and 0.80, respectively. Every record that involved a disagreement between coders was reviewed individually with two authors holding PharmD degrees and working as CPCS clinical toxicologists (RH, JL) to make a final determination about coding and develop decision rules to guide future coding. Given the relatively high initial levels of interrater reliability, after reviewing the initial 200 records, all remaining records were coded by a single author. Decision rules developed for coding included:

(a) Products denoted as "hemp" sometimes contained CBD and sometimes did not; to be conservative, records were classified as not involving CBD or a derived psychoactive cannabis product unless there was specific mention of either.

(b) If a CBD product also contained THC, it was marked as an exposure and the THC content was noted in the comments so that these records could be counted; these records were later excluded from analysis.
(c) Calls for information that also involved an exposure were included as exposures.

During the period that coders were working individually, the group met weekly to discuss any cases identified as ambiguous. The final determination of how to code these records was made jointly by two clinical toxicologists (RH, JL) working for CPCS.

Analytical strategy

We generated descriptive analyses of exposures to assess exposures, age and gender of callers, whether single or multiple substances were involved, routes of exposure, and product information where available. To assess the shift in exposures over time, we summarized the number of CBD, SCRA, and derived psychoactive cannabis product exposures by month, noting the dates of policy changes. For CBD and derived psychoactive cannabis products, the relevant data of policy change was January 2019, when the 2018 Farm Bill took effect and removed hemp-derived products with less than 0.3% delta-9 THC by weight from the Controlled Substances Act (Congress.gov 2018; National Institute of Food & Agriculture 2023). For SCRA exposures the relevant policy changes were the national Synthetic Drug Abuse Prevention Act of 2012 and California Health and Safety Code 11357.5 HSC, which took effect January 2017 and led to a statewide ban on the sale, manufacture, and distribution of these products (California Legislative Information 2017). To assess whether exposure counts changed after the implementation of these policies, we conducted interrupted time series analysis (ITSA). The ITSA model form was $Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_t + \beta_3 X_t T_t + \epsilon_t$, with β_0 as the intercept, β_1 the slope prior to policy change, β_2 the change immediately following, and β_3 the slope following policy change (Linden, 2015). Data were reported as monthly number of exposures and changes (increases or decreases) were reported as coefficients from the regression model. All analysis was conducted using Stata v17 (StataCorp LLC) (Stata Statistical Software: Release 17 [computer program] 2021).

Results

The initial search identified a total of 9,194 exposures; consistent with the coding method described in methods, each of the 9,194 call records was individually read and hand-coded by at least one investigator. Of these, 2,609 (28.4%) call records of exposures met inclusion criteria. These records included 1,460 cases (56.0%) involving exposures to CBD and 1,149 (44.0%) cases involving exposure to SCRAs or derived psychoactive cannabis products (Fig. 1).

Of the 1,460 reported exposures involving CBD, the hand-coded call record reviews found that 74 (5.1%) involved a product that contained THC. Given that these products involved traditional cannabis, which we did not anticipate would be affected by the 2018 Farm Bill policy changes, these cases were excluded from the analysis. Of the remaining 1,386 CBD exposures, 1,078 (77.8%) involved CBD alone, while the remaining 308 (22.2%) involved multiple substances (e.g., CBD and alcohol). The number of reported CBD exposures ranged from 0 to 16 annually and were highest at the end of the study time-period, in 2020 (307 reported exposures) and 2021 (337 reported exposures).

The 1,386 CBD exposures included 1,382 reports with demographic information (Table 1). Of these, individuals under age six years made up 37.8% of exposures, the highest of any age group. Many of these CBD exposures involved young children ingesting products that mimicked food such as gummies, candy, or brownies. A few cases involved young children accidentally ingesting or pouring CBD oil on themselves. Individuals aged 6 to 12 years made up 8.2% of exposures, those aged 13

Table 1
Exposures by type, age, and reported gender (reported #, percentage).

Age (years)	<6	6 to 12	13 to 17	18 to 25	26 to 50	50 (+)	Total
CBD							
Male	276 (42.1)	66 (10.1)	26 (3.9)	42 (6.4)	112 (17.1)	134 (20.4)	656 (100)
Female	247 (34.0)	48 (6.6)	27 (3.7)	34 (4.7)	153 (21.1)	217 (29.9)	726 (100)
Total	523 (37.8)	114 (8.2)	53 (3.8)	76 (5.5)	265 (19.2)	351 (25.4)	1382 (100)
SCRAs and derived psychoactive cannabis products							
Male	5 (0.6)	9 (1.0)	215 (24.6)	348 (39.8)	227 (26.0)	69 (7.9)	873 (100)
Female	3 (1.1)	2 (0.7)	86 (31.6)	76 (27.9)	80 (29.4)	25 (9.2)	272 (100)
Total	8 (0.6)	11 (0.9)	301 (26.3)	424 (37.0)	307 (26.8)	94 (8.2)	1145 (100)

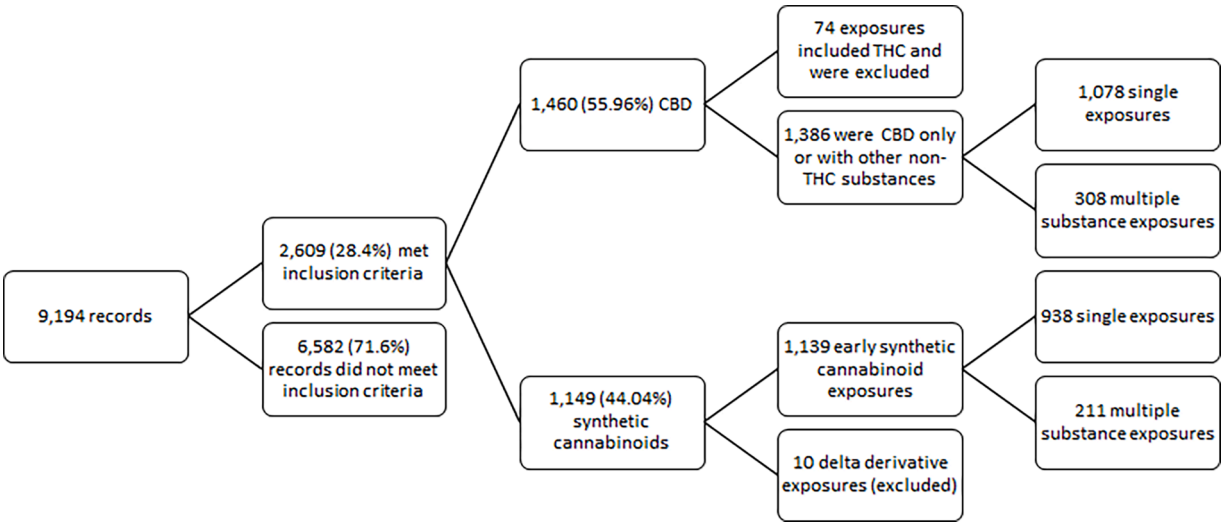

Fig. 1. Flow chart of exposure classifications.
Source: California Poison Control System; exposures hand-coded by the authors.

to 17 years made up 3.8%, those aged 18 to 25 years (young adults) made up 5.5%, those aged 26 to 50 years made up 19.2%, and those over 50 years of age made up 25.4%. With respect to self-reported gender, 47.5% of exposures were in people who identified as male and 52.5% were in people who identified as female. For these exposures, 77.8% involved a single exposure (only CBD) and 22.2% involved multiple substances. Ingestion was the most common route of CBD exposure with 1,192 (86.0%) cases; only 34 (2.5%) cases were via inhalation and 160 (11.5%) involved other routes of administration (e.g., dermal, ocular), as shown in Table 2.

The interrupted time series analysis identified that prior to the 2018 Farm Bill, the trend of reported CBD exposures was increasing significantly by 0.075 per month (CI: 0.041, 0.108). Immediately following the policy change, reported exposures increased significantly by 15.300 (CI: 11.279, 19.321). The overall trend following the policy change was a monthly increase in reported CBD exposures of 0.153 (CI: 0.035, 0.272) Results are plotted in Fig. 2.

There were 1,149 exposure reports involving a derived psychoactive cannabis product or SCRA. Among all 1,149 SCRA and derived psychoactive cannabis product exposures, 1,145 included demographic information. Among these, individuals under age six years made up 0.6% of reported exposures, those aged 6 to 12 years made up 0.9%, those aged 13 to 17 years made up 26.3%, those aged 18 to 25 years (young adults) made up 37.0%, those aged 26 to 50 years made up 26.8%, and those of 50 years of age made up 8.2%. Of the 1,145 cases, 76.2% of exposures occurred in people who identified as male and 23.8% were in people who identified as female. For SCRAs and derived psychoactive cannabis product exposures, 81.6% involved a single substance and 18.4% involved multiple substances. Unlike CBD exposures, inhalation was the most common route of SCRA or derived psychoactive cannabis product exposure with 784 (68.2%) cases, followed by ingestion with 314 (27.3%) cases, and then by other routes of administration with 51 (4.4%) cases.

Our individual reading of each call record found that 383 of these exposures indicated a product name; these were 294 (76.8%) reported exposures listed as “spice”, 51 (13.3%) as “incense”, 28 (7.3%) as “potpourri”, and 10 (2.6%) as “delta” (hemp-derived). For the 10 (0.9%) exposure reports that specifically referenced a derived psychoactive cannabis product, all were in 2021 (6 reports) and 2022 (4 reports). Seven (70%) of these cases involved a derived psychoactive cannabis product only, and 3 (30%) involved multiple substances. The most serious clinical outcome was in a 3-year-old child that consumed cookies containing 62.5mg delta-8 THC (single exposure, unintentional) and was admitted to the hospital; a second other case resulted in admission to a health care facility and involved an older adult (50+) that consumed delta-8 gummies (and CBD, intentional). There were insufficient cases to conduct an interrupted time series analysis specific to derived psychoactive cannabis products.

The remaining 1,139 (99.1%) exposure reports referenced SCRAs. The interrupted time series analysis identified that prior to July 2012, the trend of monthly reported SCRA exposures was increasing significantly by 1.040 (CI: 0.860, 1.219). Immediately following the federal policy change in July 2012, reported exposures decreased significantly by 18.444 (CI: -25.431, -11.450), then exposures continued to significantly decrease each month by 1.254 (CI: -1.487, -1.021). There was no immediate change in exposures following California state ban on SCRAs. The overall trend for both policy changes was a monthly decrease in reported SCRA exposures of 0.214 (CI: -0.367, -0.061) Results are plotted in Fig. 3.

Discussion

Understanding the shift in cannabis-related exposures in California provides potential regulatory guidance for other areas where derived cannabis products are marketed and that may have experienced increased exposures. As anticipated, we identified a significant increase in CBD exposures after the removal of hemp products from the Controlled Substances Act. Our finding that many CBD exposures among young children involved ingestion of products that looked like candy is consistent with previous research on traditional cannabis exposures, which has found that young children may confuse cannabis products such as gummies with actual food, and consume more than a single dose as a result (Cao et al., 2016; MacCoun & Mello, 2015; Richards et al., 2017; Roth et al., 2022; Tsutaoka et al., 2018). Our reading of case reports for adults also identified multiple instances where people stated they confused CBD gummies for normal candy and ingested more than a single dose as a result. As prior studies have noted, this mistake may be associated with packaging that does not clearly distinguish cannabis products from food (Cao et al., 2016; Coret & Rowan-Legg, 2022; Tsutaoka et al., 2018), and suggests a potential need for additional regulation in this area.

Despite our expectations, we identified few reported exposures involving derived psychoactive cannabis products such as delta-8, delta-10, or HHC. Multiple popular media reports have noted safety concerns related to derived psychoactive cannabis products marketed as being derived from hemp (Casacchia, 2023; Kary, 2023). After the change in regulatory status for derived cannabis products in 2018, derived psychoactive cannabis products are commonly sold with higher levels or THC analogs such as delta-8 THC than are permitted for traditional cannabis products containing delta-9 THC (Heidelbaugh, 2023; Nieto--Munoz, 2023). Previous research on traditional cannabis exposures identified that some SCRA and derived psychoactive cannabis products were coded as traditional cannabis in poison control records; (Roth et al., 2022) this may reflect limited awareness that these products are different from traditional cannabis on the part of patients, providers, or poison specialists receiving calls. The mismatch between popular reports of poisonings associated with derived psychoactive cannabis products (Kary, 2023; U. S. Food & Drug Administration 2022) and exposures reported to CPCS suggests that improvements in surveillance may be needed to accurately assess health risks.

Surveillance over time of SCRAs (e.g., Spice) suggests that these products were used primarily by young adult men (Law et al., 2015), and our results were consistent with this expectation. Overall exposures in our sample dropped significantly after federal and state regulation intended to deter use. Nonetheless, people making calls to CPCS reported secondhand exposures to SCRAs, edible formulation exposures, long-term reactions, addiction, and relapse even after regulations took effect. The severity of health outcomes associated with SCRAs (Darke et al., 2020; Riederer et al., 2016; Spaderna et al., 2013; Trecki et al., 2015; Wiebelhaus et al., 2012) suggests the need for continued enforcement of current laws to deter use. The association between increased regulation and a reduction in reported exposures suggests that changing federal and state policies has promise as a strategy to reduce accidental and intentional use of CBD and derived psychoactive

Table 2
Exposures by type, number, and route (reported #, percentage).

	Number of substances			Route of exposure			
	Single	Multiple	Total	Inhaled	Ingested	Other	Total
CBD	1078 (77.8)	308 (22.2)	1386 (100)	34 (2.5)	1192 (86.0)	160 (11.5)	1386 (100)
Synthetic cannabinoids	938 (81.6)	211 (18.4)	1149 (100)	784 (68.2)	314 (27.3)	51 (4.4)	1149 (100)

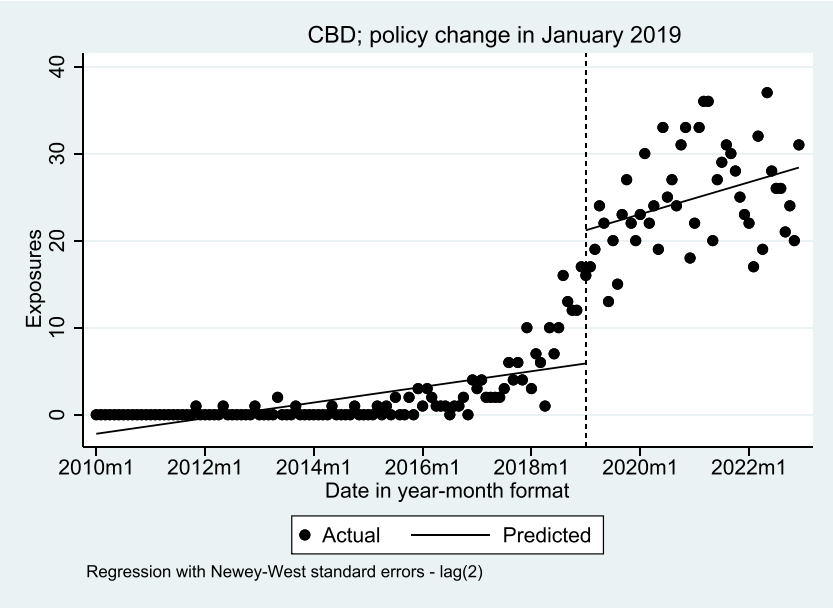

Fig. 2. CBD interrupted time series analysis, 2010-2022.
Source: California Poison Control System; exposures hand-coded by the authors.

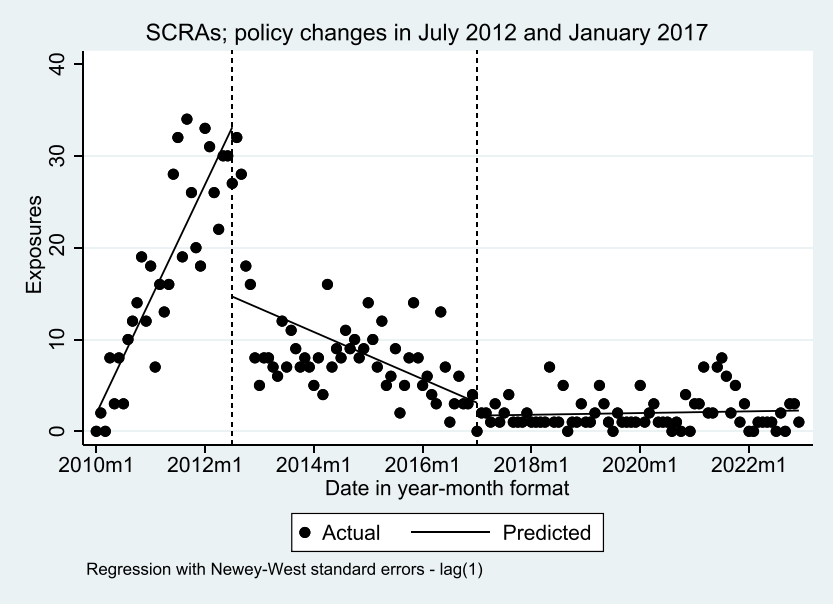

Fig. 3. SCRA interrupted time series analysis, 2010-2022.
Source: California Poison Control System; exposures hand-coded by the authors.

cannabis products.

Our study has limitations. The data provided by the CPCS is limited to cases reported in California. Moreover, the data gathered by CPCS only includes the cases volunteered by patients and providers. However, at the national level, prior research has found that approximately half of all toxic exposures are reported to a state poison control center, although this finding was not specific to drugs (Guyer & Mavor, 2005). Over time, health care provider calls to poison control may decline due to increased familiarity with initially novel products and their health effects; however, this behavior change, if it exists, would not explain the low number of exposures reports we found for derived psychoactive cannabis products. Our study was observational and as a result, we can only identify associations between policy changes such as the 2018 Farm Bill and reported CBD exposures, rather than causality. Our categorization of exposures was limited to information received by CPCS poison specialists and information known to callers. In multiple cases, the terms cannabinoid, cannabidiol, cannabis, and marijuana were used interchangeably, requiring a detailed reading of call records to classify exposures. Limited awareness of distinctions between traditional cannabis products and derived psychoactive cannabis products may have contributed to misclassification. Overall, these limitations suggest that our findings have likely underestimated the actual number of relevant exposures and their associated health risks.

There have been recent efforts by the US DEA to further regulate derived psychoactive cannabis products, specifically delta-8 and THC-O (US Food & Drug Administration 2023). However, it is unclear to what extent this effort may affect exposures, given that these products have been marketed as legal for several years. In addition, multiple derived

psychoactive cannabis products were not named by the DEA.

Conclusions

Overall, our findings suggest areas of potential concern regarding increases in exposures to CBD and limited information about derived psychoactive cannabis products such as those containing delta-8. CBD exposures significantly increased following the federal reclassification of hemp products, while current surveillance data appear to provide little or no information about derived psychoactive cannabis products. More promisingly, reported exposures to SCRAs decreased following policy changes. These findings suggest a need for improved data collection, increased guidance for health communication, as well as support for potential regulatory changes identified in previous research, such as stronger packaging and potency restrictions. Modifying existing surveillance strategies would provide more information on use of derived cannabis products marketed as originating from hemp. In the interim, limited regulation of these products increases their accessibility and the increase in unintentional CBD exposures among children suggests an immediate need for clinicians to inform parents of their potential risks and advise safe storage of these products.

Funding

Unfunded research.

Ethical approval and protection of human participants

This research was approved by the University of California San Francisco (UCSF) Institutional Review Board on December 9, 2022 (#20-32966).

CRediT authorship contribution statement

Kunal Madan: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Samantha Schmidt:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Raeiti Fouladi Chami:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Raymond Ho:** Conceptualization, Validation, Investigation, Resources, Writing – review & editing, Supervision. **Justin C. Lewis:** Conceptualization, Validation, Investigation, Resources, Writing – review & editing, Supervision. **Dorie E. Apollonio:** Conceptualization, Methodology, Software, Data curation, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge Terry Carlson for his assistance in extracting CPCS records.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2023.104313.

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