Health Effects of High-Potency Cannabis Products: A Scoping Review

HB 21-1317 Report to the Colorado Legislature, July 1, 2022

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Submitted to:

House Finance and Public and Behavioral Health and Human Services Committees

and

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Table of Contents

Executive Summary of Report

Introduction

Colorado House Bill 21-1317 (HB 1317) (CONCERNING THE REGULATION OF MARIJUANA FOR SAFE CONSUMPTION, AND, IN CONNECTION THEREWITH, MAKING AN APPROPRIATION) requires the Colorado School of Public Health to "…do a systematic review of the scientific research related to the physical and mental health effects of high-potency THC marijuana and concentrates." On receiving funding from the state in July 2021, the Colorado School of Public Health (ColoradoSPH) established a multidisciplinary team to carry out a review of the available literature with the intention of identifying the extent of the available literature, its characteristics, and its potential utility for addressing the scientific questions underlying the request made in HB 1317. As directed by the bill, the ColoradoSPH established the required Scientific Review Council (SRC) and set up a website to make its work products readily available to the public. This report describes progress on the review task through June 30, 2022.

The team quickly determined that a comprehensive systematic review had not yet been undertaken that covered the mandate of HB 1317 and that there was substantial uncertainty as to the scope and state of the literature on high-concentration[1] cannabis and concentrates as a result. Consequently, a decision was made to carry out a scoping review that would provide a searchable catalogue of the evidence. The resulting database could then be used to structure further systematic reviews along with meta-analyses and modeling to probe quantitative relationships. Further shaping the strategy was the enormous body of literature identified initially—over 46,000 titles and abstracts.

Methods

For the purpose of literature searching, the scoping review had the following two goals: 1) identify and describe studies that explore the relationship of high-concentration cannabis products with beneficial and adverse health outcomes; and 2) identify and describe studies that report adverse effects of exposure to high-concentration products (with no comparison group). A search strategy was developed to identify all relevant studies by an experienced medical information specialist and multiple databases were searched. In general, the conduct of the review followed the state-of-practice for systematic and scoping reviews. A protocol was developed, comments were solicited from the SRC and the public, and the protocol was published. Training for the screeners and data extractors has been standardized and quality control measures have been in place throughout. The title and abstract screening was accelerated by using artificial intelligence algorithms built in a screening tool called DistillerSR.

The literature searches resulted in 46,004 unique titles and abstracts that were narrowed to the 753 studies by a two-step screening process. The initial target for data extraction is 489 studies,

[1] Throughout the report, *concentration* is used instead of *potency* as the scientifically correct word. The ColoradoSPH team recognizes that potency is widely used, including in the title of HB 21-1317, but from a pharmacological perspective, potency refers to the activity of an agent and not its concentration.

including observational studies and randomized trials. Subsequently, we will address the case reports and case series and systematic reviews. An extensive set of items on study characteristics, exposures, and outcomes were extracted following a standardized and quality-assured process. We collected data on THC concentration using the units and measures as reported in the included study.

Results

The 489 studies included at present were evaluated on overall study objectives: efficacy of a product for a therapeutic indication (24%), harm/safety (45%), and both (32%). The included studies (n=489) were separated by study design: randomized control trials (37%) and observational studies (60%), with 15 other studies that were undefined (3%). The included studies were conducted across multiple countries, primarily in the United States (46%), the United Kingdom (11%), and Canada (11%). Within the US, studies were done primarily in California (n=54), Colorado (n=28), and New York (n=18). The study populations were variable in characteristics, including ages from newborn to adults over 65, with a range of racial and ethnic groups. Of the studies included, funding source, author affiliations, and conflicts of interest were recorded. Information was lacking for some studies; 114 studies did not report their funding source (23%) and 189 studies did not report if authors had conflicts of interest (39%). Measures relevant to health equity were also noted, but only 67 studies included analysis on any measure of health equity (14%). Fifty-seven studies included analysis or stratification of subgroups (12%), 11 studies focused exclusively on historically excluded populations (2%).

We created an evidence map for visualizing the studies identified in the scoping review. For that purpose, we use a publicly available Tableau dashboard so that studies can be sorted by study characteristics, exposures, and outcomes. As of June 22, 2022, we have completed and verified data extraction for exposures and outcomes for 68 studies so that we have an initial but partial view of the exposures and outcomes covered in the scoping review. Cannabis products in included studies were used for medicinal (54%), recreational (26%), unintentional (4%), and other (12%) purposes with 13 studies not reporting the purpose of cannabis use (23%). Fifty studies reported a route of administration, including inhalation (68%), ingestion (44%), and other (33%). There was a large amount of variability in reporting of THC concentration, including the units reported and the indices used. The mean THC concentration for studies reporting % THC was 32% THC. Forty-eight studies (84%) reported the frequency of intake, with the most common frequency being daily (26%), and 41 studies reported the duration of intake.

The most common outcome domain for included studies was mental health (49%), followed by pain (33%), sleep (25%), substance use / substance dependence (21%), gastrointestinal (19%), neurological (19%), psychosocial (16%), cardiometabolic (9%), injury and death (5%), respiratory (5%), cancer (4%), ocular (4%), and sexual health and reproductive health (2%). Seventeen studies (30%) included a direct association between THC concentration and health outcomes. Eleven studies (19%) included a direct association between concentrates and health outcomes.

Discussion of Findings and Next Steps

We have attempted to identify all relevant and accessible literature on the effects of high-concentration THC products. To date, such a review has not been undertaken. The support for the ColoradoSPH under HB 1317 has facilitated a needed systematic review and the creation of a database that will support further work by the review team and others who will use the publicly accessible database resource. The systematic review task designated to the ColoradoSPH under HB 1317 proved to be enormous. The team initially identified 46,004 titles for screening and then moved through the review process to arrive at the 753 articles for data extraction. Our review encountered the previously identified challenges of the research literature on cannabis products and high-concentration THC products in particular. The deficiencies we noted went beyond the characterization of exposure to THC products and determinants of dose to such critical items as basic descriptors of study population characteristics and methods.

As this report is written, the ColoradoSPH team is moving towards completion of data extraction from the 489 studies with information on exposures and outcomes. With completion of data extraction during July 2022, next steps will utilize the evidence map to:

- Examine the exposure/outcome pairs and assess the availability of data relevant to the review's main questions;
- Determine if there is sufficient evidence to warrant focused systematic reviews that would address high-concentration THC products;
- Characterize critical research gaps.

We plan a follow-up report to be submitted in September 2022 after data extraction is complete and the findings from the resulting database have been fully assessed. That report will set out a complete roadmap for next steps in the review process including the anticipated products and the schedule for submitting them to the legislature. We recognize that submission in advance of the 2023 General Assembly is needed. In tandem with the SRC, we anticipate making recommendations in the follow-up report that will suggest directions for future research and for improving the quality of research.

Introduction

HB 21-1317 Charge to the Colorado School of Public Health

Colorado House Bill 21-1317 (CONCERNING THE REGULATION OF MARIJUANA FOR SAFE CONSUMPTION, AND, IN CONNECTION THEREWITH, MAKING AN APPROPRIATION) requires the Colorado School of Public Health to "…do a systematic review of the scientific research related to the physical and mental health effects of high-potency THC marijuana and concentrates." This review will include "…all available scientific evidence-based research regarding the possible physical and mental health effects of high-potency[2] THC marijuana and marijuana concentrates regardless of the location of the research." "The research must study the effect of high-potency THC marijuana on the developing brain and the effect of marijuana concentrates on physical and mental health." "The research must systematically curate and synthesize existing research, identify evidence gaps, and identify new research that is needed to better understand the health implications of high-potency THC marijuana products and the specific THC potency levels and amounts at which various health concerns arise." This research will inform a public health campaign "…regarding the effect of high-potency marijuana on the developing brain and mental health." The research will also inform rules for prescriptions to indicate "…maximum THC potency level of medical marijuana being recommended" and a level for THC toxicity screening.

ColoradoSPH Review Team and SRC Members

Table 1 lists the members of the Cannabis Research & Policy Project Team (Table 1), and Table 2 provides the Scientific Review Committee Members (Table 2).

ColoradoSPH Review Team

In response to this charge from the Colorado General Assembly and on receipt of funding in July 2021, the Colorado School of Public Health (ColoradoSPH) immediately assembled a systematic review team, drawing on expertise within the school and the University of Colorado School of Medicine (Table 1). The resulting team, led by Dr. Jonathan Samet (Professor and Dean of the ColoradoSPH) along with Dr. Gregory Tung, includes faculty with expertise and substantial experience in the conduct of systematic reviews (Drs. Bero and Li), faculty with expertise and experience related to cannabis and THC (Drs. Brooks-Russell and Wang), staff with expertise in the methodology of systematic reviews (Lawrence, Leslie, Oberste, and Dr. Rittiphairoj), and ColoradoSPH students who screened studies and extracted data.

Background on Systematic Review and Scoping Review

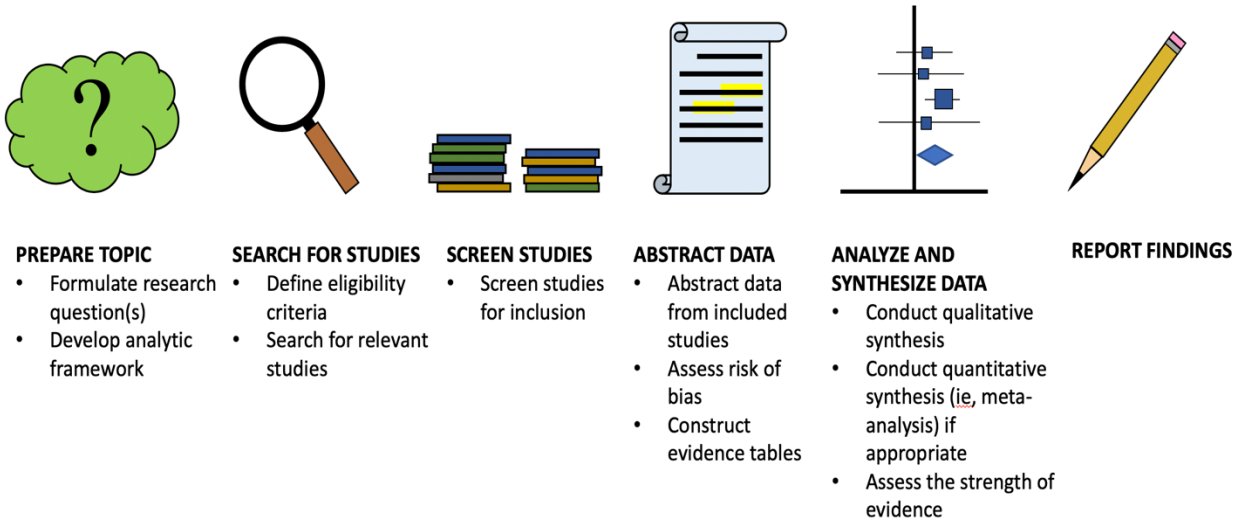
House Bill 21-1317 called on the Colorado SPH specifically to carry out a systematic review. A systematic review attempts to identify, appraise, and synthesize all available evidence that meets pre-specified eligibility criteria to answer a specific research question (Figure 1). A systematic

[2] As explained subsequently, for scientific correctness, the term concentration will be used throughout this report rather than potency.

review may or may not include a meta-analysis, which is the quantitative synthesis of the results from multiple independent studies. Scoping reviews are helpful precursors of systematic reviews because they map the literature on a particular topic or research area and provide an opportunity to identify key concepts, gaps in the research, and types and sources of evidence to inform practice, policymaking, and future research.

A systematic evidence map can be a major output of a scoping review. Systematic evidence mapping is a methodology adapted from the social sciences and frequently employed in environmental health. The aim of the systematic evidence map is to characterize the evidence base on a particular topic through an interactive interface using data visualization (Wolffe et al., 2019). The results of scoping reviews can be presented in static tables, but there are advantages to creating an evidence map. The systematic evidence map is a queryable database that can allow users to explore questions according to their own research or policy interests that may not have been posed initially in the scoping review. Although evidence maps often take longer to produce than a static scoping review, they create an evidence surveillance resource with application beyond the scoping review question and one that can be updated periodically as new research becomes available.

Figure 1: Step by step overview of systematic review process (Li et al., 2021).



Considerations Related to Strength of Evidence and Decision-Making

To reiterate an element of the charge to the ColoradoSPH in HB 1317: "The research must systematically curate and synthesize existing research, identify evidence gaps, and identify new research that is needed to better understand the health implications of high-potency THC marijuana products and the specific THC potency levels and amounts at which various health concerns arise." The findings related to the health implications and THC concentration and levels at which effects occur have potential regulatory implications as well as guiding the content of the educational campaign.

One critical element of using evidence from a systematic review for such purposes is judging the strength of the evidence identified; that is, providing a determination of how strongly the evidence addresses the questions raised in HB 1317 while also gauging the complement of strength of evidence and the degree of uncertainty. In considering the need for regulation based on this review and other information, our recommendations will take into account the degree of certainty of conclusions on the existence of adverse and beneficial effects. Judgments on the strength of evidence are typically made by expert groups, in the instance of this systematic review by the ColoradoSPH team with input from the SRC. Descriptions of strength of evidence are qualitative and expressed with such terminology as weak, suggestive, moderate, and strong or other ranked scales. In the event that the available evidence supports one or more systematic reviews, our approach to evaluating strength of evidence will be described in advance, along with the scale used to describe it.

Overview of Approach

In addressing the charge provided by HB 1317, the ColoradoSPH team followed the directions of the bill, implementing a systematic review following the procedures that reflect the state-of-practice. The team quickly determined that a comprehensive review had not yet been undertaken that covered the mandate of HB 1317 and that there was substantial uncertainty as to the scope and state of the literature on high-concentration cannabis and concentrates as a result. For example, it was uncertain as to whether studies would provide data suitable for modeling dose-response relationships of the occurrence of effects with concentration or identifying threshold levels above which harms manifest.

Consequently, a decision was made to carry out a scoping review that would provide a searchable catalogue of the evidence. The resulting database could then be used to structure further systematic reviews along with meta-analyses and modeling to probe quantitative relationships. Further shaping the strategy was the enormous body of literature identified, initially—over 46,000 titles and abstracts. The number of studies potentially needing consideration provided a further rationale for the approach taken, given the effort required to extract data from studies. Given the size of the task, a large team, including over 15 ColoradoSPH students, has been in place for the project.

In general, the conduct of the review has followed the state-of-practice for systematic and scoping reviews under the direction of Drs. Bero and Li. A protocol was developed, comments solicited from the SRC and the public, and the protocol was published. Training has been standardized and quality control measures have been in place throughout. The title and abstract screening was accelerated by using artificial intelligence algorithms built in a screening tool called DistillerSR. Throughout, a publicly accessible website has provided information concerning the SRC's meetings and its comments and the review. In the interest of transparency, all of the SRC meetings were open to the public and meeting notes and slides were posted to the project website. In addition, our review protocol and all revisions as well as background materials are all available on the project website. The project website also allowed for public comments to be submitted and a member of our project team reviewed all submitted comments. The overall project team meets twice per week with multiple additional topic-focused meetings.

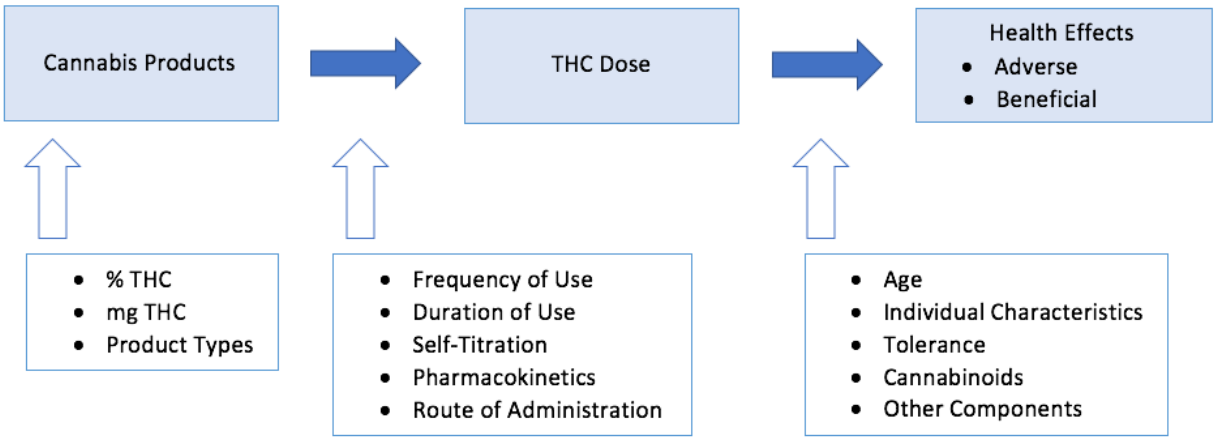
A Framework for How High-Concentration THC Cannabis is Related to Health Effects

The ColoradoSPH was charged with addressing high-potency THC cannabis products and concentrates. As with other efforts to assess the effects of using high-concentration products, e.g., the Colorado Department of Public Health and Environment (CDPHE), the review team interpreted its charge as considering how effects (whether harms or benefits) depend on the concentration of THC in the product used. In pharmacological terms, *potency* is defined by the U.S. Food and Drug Administration (FDA) as: "The specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result (FDA, 2022)." This definition separates pharmacological activity from the amount of an agent entering a person. Following CDPHE's 2020 report from the Retail Marijuana Public Health Advisory Committee, we consider THC concentration to be the indicator of "potency" as reflected in the language of HB 1317 (Holdman et al, 2020). Concentration is the THC percentage by volume for vaped liquids and the THC percentage by weight for edible products. Per the language of HB 1317, we will use the term "high-concentration" when referring to "high potency" products. Cannabis potency is often not defined by the intensity or strength of clinical effect as it may be used when comparing pharmaceuticals, such as with different opioids (e.g., fentanyl vs morphine). Furthermore, there is no universal definition of a cutoff value to define a high-concentration cannabis product. The overall THC concentrations of cannabis flower and the related products have increased over the past several years. Confiscated cannabis from the Drug Enforcement Administration from 1995 to 2014 has demonstrated an increased in THC content from 4% to 12% (Elsohly et al., 2016). In Colorado, cannabis flower had an average of 20% THC (upper limit of 35%). Concentrate products have increased THC concentration from 50% to nearly 70% in recent years (MPG Consulting, Leeds School of Business University of Colorado Boulder, 2020). A recent study found that over 90% of products sold in the retail cannabis dispensaries were > 15 % THC (Cash et al., 2020).

To address the question of the harms and benefits of high-concentration products, this review categorizes THC concentration in products used in the research identified while also taking into account the route of use, the frequency of use, and the amount used. The relationship between THC concentration in a product and health effects is complex and influenced by these modifying factors related to use, along with the tolerance of the individual using the product. Generally, in conceptualizing how environmental exposures (consider cannabis and high-concentration THC products as such) increase risk for various health effects, whether harmful or beneficial, a paradigm involving exposure, dose, and risk is often applied (Figure 2a). Exposure constitutes the contact of the agent with people; dose is the amount of the agent that enters the body; and risk is the probability that an event will occur. In a relevant example, we are all exposed to ambient or outdoor air pollution (the exposure, referring to what is in the air) and we inhale the air pollutants, such as small particles, into our lungs (the dose, referring to what is taken into the body), leading to increased risk for various adverse health consequences, such as worsening of asthma and even increased risk for dying.

Figure 2a: Illustrates how environmental exposures increase risk for various health effects, whether harmful or beneficial, a paradigm involving exposure, dose, and risk is often applied.

Figure 2b: Illustrates the paradigm to high-concentration cannabis products.



In Figure 2b, we generalize this paradigm to high-concentration cannabis products. The cannabis product now represents exposure while dose refers to the amount of THC entering the body, by any route. Risk refers to the likelihood of occurrence of potential outcomes related to exposure and the attendant doses. The characteristics and the concentration of the product are critical to determining THC dose. When comparing similar use patterns and characteristics with two different strength products, certainly the higher concentration product will lead to a higher THC dose. However, many factors impact the dose reaching the brain. Patterns of use (infrequent or chronic) will significantly impact dose and affect risks for short-term and long-term health outcomes. Differences in bioavailability and pharmacokinetics between routes of exposure (e.g. inhalation or ingestion) will also affect systemic absorption, dose, and ultimately health outcomes. The dose of THC that reaches the receptors in the brain will vary with the way that each individual reacts to the product and particularly how the THC is distributed and metabolized, i.e., the pharmacokinetics. As implied by Figure 2b, the effects on health will vary with the characteristics of the individual using the product and the tolerance of the individual, and they need to be considered in the context of the purpose for which the product is used, particularly recreational or therapeutic.

An individual's tolerance to the effects of THC, similar to other drugs, can change the amount and/or frequency used by an individual. In an experienced user, tolerance can lead to increased frequency of use, or use of higher concentration products to obtain the desired effects. People who use cannabis may also self-titrate to the desired effect regardless of concentration or product used. Similar doses in an individual naïve to cannabis use can lead to stronger effects or

undesired adverse effects. As experienced with other substances, use of higher concentrations of drugs with abuse potential can lead to addiction and dependence. This dose dependence of abuse liability has contributed to the concern about exposure to high THC concentrations.

Finally, the cannabis plant can provide about 100 different cannabinoids besides THC, and many other constituents including terpenes, potential contaminants, and other naturally occurring entities. Several commercially available products contain different mixtures and fractions of these various cannabinoids and constituents, often combining THC with CBD. Some research studies have considered products with varying amounts of THC and other cannabinoids such as CBD. How the various cannabinoids and other constituents interact with each other, perhaps magnifying or attenuating effects, has not yet been well studied. Although many consumers and commercial cultivators promote the assumption that the mix of cannabinoids may influence effects of products, the interactions of the cannabinoids with the potential for synergistic, or antagonistic effects, have not been well characterized.

Variation in Effects Across Populations

The population of Colorado is diverse in numerous respects potentially relevant to exposure to and utilization of high-concentration cannabis products as well as potential health effects. Health equity is a driving concern in public health and a topic to be considered in this systematic review. Consequences of use of these products may differ in groups defined by income and education group, race and ethnicity, and geographic location, e.g., urban or rural. Understanding how effects reach to different groups within the population is essential in determining if high-concentration cannabis and THC contribute to health disparities. Consequently, characteristics of populations included in the studies reviewed will be captured to the extent that they are provided.

Methods

Protocol Summary

The draft protocol for the scoping review was developed by the review team, posted for public comment, and discussed by the Scientific Review Committee on June 8, 2022, June 15, 2022, June 21, 2022, and June 29, 2022. Based on this initial feedback, revisions to the protocol were made, as detailed here.

- A decision to include case series and case reports in the scoping review.
- The categorization of high-concentration products was expanded to include categories for higher mg or % THC beyond those originally specified, and a category added for high-concentration products when THC content was not specified.
- Examples of health outcomes that are eligible for inclusion in the review were not characterized as beneficial or harmful (Table 3).
- Text was modified to clarify that race, ethnicity, disadvantage and other correlates of health disparities would be considered during data extraction, analysis, and synthesis.

The full protocol is published and available as:
Bero, L., Li, T., Leslie, L., Rittiphairoj, T., Piper, C., Wang, S., … Samet, J. (2021, December 11). Health Effects of High-Potency Cannabis Products: A Scoping Review Protocol. https://doi.org/10.17605/OSF.IO/WV7E9

Research Question and Objectives

The scoping review aims to:

- Identify and describe studies that explore the relationship of high-concentration cannabis products with beneficial and adverse health outcomes.
- Identify and describe studies that report adverse effects of exposure to high-concentration products (with no comparison group).

Eligibility Criteria

We included human studies without any restrictions by age, sex, gender, health status, country, state or specific demographics. We also included studies conducted in any country and research reports on recreational/non-prescription cannabis use and/or medicinal cannabis use. We included studies of cannabis exposure taken by any route of administration if a THC concentration was reported using a number with associated units (e.g., 25% THC or 2 mg THC). We also included studies without a reported THC concentration if the study could be reasonably inferred to address a high-concentration product based on method of use (e.g., vape, dab) or on product type (e.g., wax, butane hash oil). No restrictions were made based on product type, route, frequency, or specific THC levels. We excluded studies with only non-THC cannabinoid exposures (e.g., cannabidiol, cannabinol). We excluded studies of dronabinol, nabilone, and other orally administered synthetic cannabinoid products for medicinal use only.

We included studies of any health outcomes regardless of whether they were classified as beneficial or adverse. This includes outcomes that may highlight disproportionate effects by race,

ethnicity, or indicators of disadvantage. Table 3 summarizes some examples of outcomes that have been described in various reports. This list is not intended to be inclusive of all outcomes that have been identified in this review. For example, we also included studies that measured mechanistic outcomes, psychomotor effects or indicators of neurocognitive function, such as psychomotor performance, memory, binocular depth, motor control, response time or neurocognitive impairment. We excluded studies that measured physiological indicators without any particular health implications, such as body temperature, heart rate, or blood pressure.

We included studies of any design (randomized controlled trials, cohort studies, case-control studies, case reports, and case series). We also included systematic reviews and meta-analyses of any design, including reviews of poison center reports. We excluded study protocols, narrative reviews, meeting abstracts, comments, editorials, interviews, letters, and non-English publications. We excluded animal studies, as well as laboratory or simulation-based studies not conducted in humans.

Search Strategy

An experienced medical information specialist designed a comprehensive search strategy that was peer reviewed by a second medical information specialist prior to executing the search. We limited the searches to the English language and human studies when possible. We excluded comments, editorials, interviews, news articles, and letters as publication types when possible. We did not apply any date limitation. We developed the search initially for Ovid MEDLINE and translated the search to the other databases. Details of the search strategy are available in the protocol.

We searched the following databases on October 5th, 2021: Ovid MEDLINE All (1946 to October 5, 2021), Embase (via Elsevier, Embase.com, 1947 to October 5, 2021), AMED (Allied and Complementary Medicine via Ovid, 1985 to October 5, 2021), Cochrane Library (via Wiley, including Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), Database of Abstracts of Reviews of Effects (DARE, 1995 – March 2015, via crd.york.ac.uk), CINAHL (Cumulative Index to Nursing and Allied Health Literature via EBSCOhost, 1981 to October 5, 2021), and ToxLine (via Pubmed.gov using the ToxLine subset).

Study Selection

We imported search results into DistillerSR, a program used for screening and data extraction for systematic reviews. The search records were deduplicated prior to screening. DistillerSR has several Artificial Intelligence (AI) features for accelerating screening and performing quality checks. We piloted screening forms and used training sets to assure both human and AI screening operationalized the eligibility criteria appropriately while reviewing the titles and abstracts. Titles and abstracts were screened in duplicate; after 1,000 records the AI tool acted as the second screener for the likely ‘includes’ and ‘excludes’. Two human screeners performed full-text screening. Throughout these steps, discrepancies between inclusion decisions were resolved by a senior reviewer. We performed quality checks for screening errors weekly.

Data Extraction

We developed a draft list of data extraction elements and received feedback from the Scientific Review Council. The data extraction items are based on our protocol and were selected to assure that we can address all questions posed in the analysis section. Table 4 provides the condensed list of data extraction elements, see protocol for the comprehensive data extraction forms. The data extraction items were pilot tested before being incorporated into the DistillerSR software. We prioritized studies for data extraction based on relevance to the review question (e.g., relevant to high-concentration THC). One person performed data extraction and a senior reviewer verified the data for quality assurance.

We collected data on THC concentration using the units and measures as reported in the included studies. We collected data from reports that measure THC concentration in different ways; for example, as blood levels of THC or mg THC in products consumed. Most reports refer to content of THC in the cannabis product as either a percentage THC or mg per serving for edible products, although some estimated mg of THC for smoked products as well. These amounts could be reported over different periods of time (e.g., a month or a week) and consequently the time frame was also recorded. The highest and the lowest values were extracted.

Synthesis

Study characteristics are reported descriptively as the number of studies with the particular attribute. Quantitative synthesis, such as meta-analysis, could not be undertaken in this initial review because of the heterogeneity in the study designs, populations, exposures to cannabis, and outcomes. The wide range of outcomes and inadequacies in reporting in many studies also limited the possibility of calculating effect sizes or other meaningful quantitative summaries of associations. Consequently, studies that were similar to each other were grouped and the evidence was qualitatively synthesized, following the guidance outlined in 'Chapter 12. Synthesis using other methods' of the Cochrane Handbook for Systematic Reviews of Interventions (McKenzie, Brennan, 2022).

Evidence Map

We created an evidence map for display in a publicly available Tableau dashboard. Tableau is a software data visualization software commonly used to build interactive dashboards. A Tableau Dashboard is well suited to the type of information gathered in a Scoping Review, as the studies that have been characterized can be explored in many ways depending on the purposes of the user. The dashboard is organized so that studies can be sorted by study characteristics, exposures, and outcomes. In addition, the dashboard allows for identification of studies based on any combination of data elements extracted.

To describe the studies identified for data extraction, the evidence map was interrogated to answer a range of questions about the evidence, such as:

1. Of the different types of cannabis products studied, how many have reported THC concentration, frequency, and/or duration?

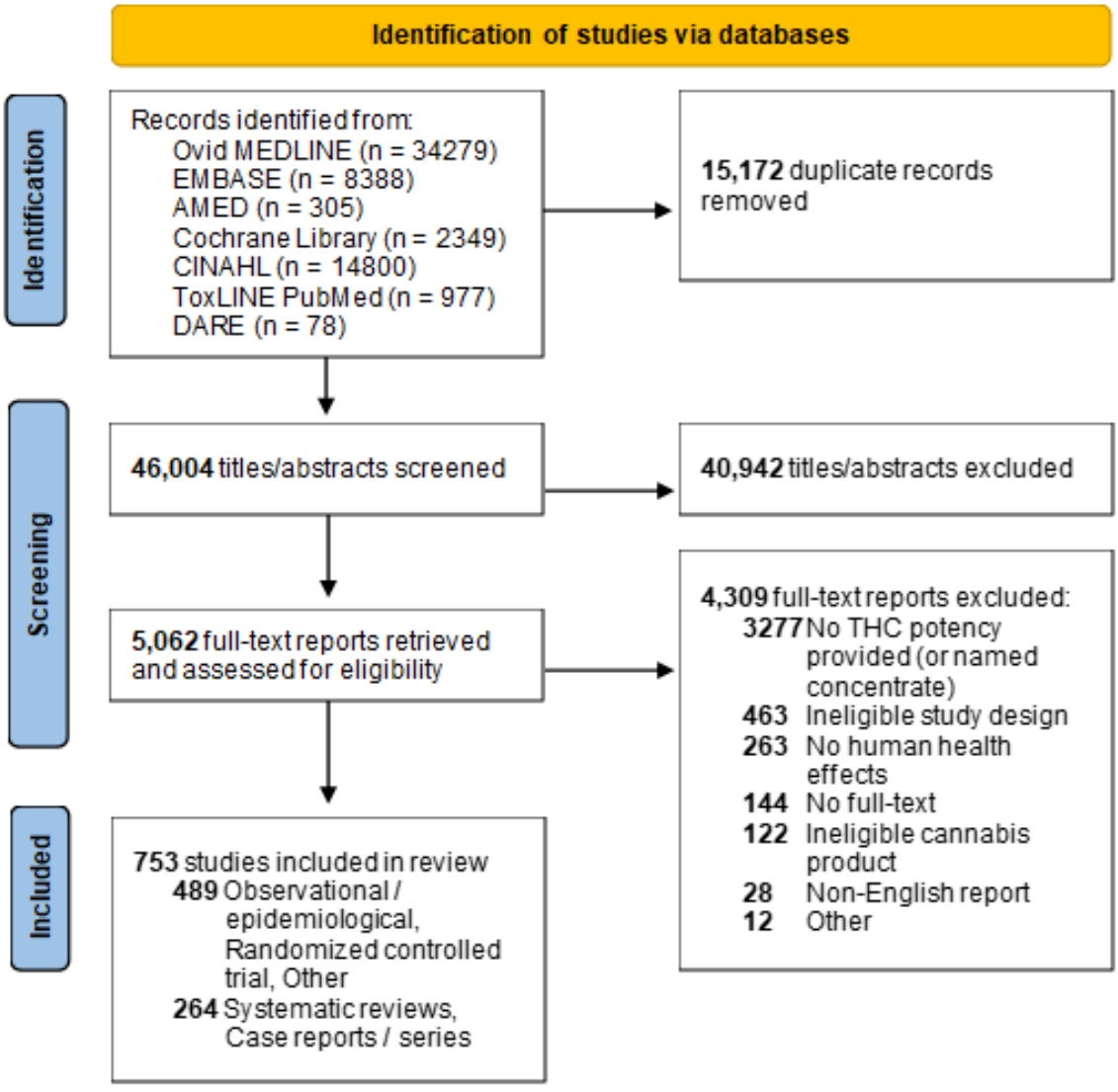
2. What types of outcomes have been examined for studies that reported THC concentration?
3. What types of outcomes have been studied for the different types of cannabis products?
4. What potencies have been reported in the literature?
5. What potencies have been studied by outcome?

Results

We followed the checklist for reporting the conduct of a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews (PRISMA-ScR) (Tricco et al., 2018).

The search and selection process of a systematic review is captured in a PRISMA flow diagram (Figure 3), which describes the flow of study selection from the initial literature search to the final selection of articles for inclusion and data extraction. Figure 3 provides a PRISMA diagram for this review as of May 24, 2022. The literature searches resulted in 46,004 unique titles and abstracts that were narrowed to the 753 studies in the scoping review. The initial target for data extraction is 489 studies, including observational studies and randomized trials. Subsequently, we will address the case reports and case series and systematic reviews.

Figure 3: PRISMA diagram outlines the study selection starting from initial literature searches to the final literature sources used for data extraction.



Characteristics of Included Studies

Table 5 presents a summary of the study characteristics for the 489 observational and randomized controlled trials. The characteristics of the 264 systematic reviews, case reports, and case series will be similarly documented. The 489 included studies were evaluated on overall study objectives: efficacy of a product for a therapeutic indication (24%), harm/safety (45%), and both (32%). The included studies (n=489) were separated by study design: randomized control trials (37%) and observational studies (60%), with 15 other studies that were undefined (3%).

The included studies were conducted across multiple countries, primarily in the United States (46%), the United Kingdom (11%), and Canada (11%). There was at least one study from 22 other countries. Within the US, studies were done primarily in California (n=54), Colorado (n=28), and New York (n=18), but participants from all 50 states were involved in at least one study. The study populations were variable in characteristics, including ages from newborn to adults over 65, with a range of racial and ethnic groups. Some studies also had restrictions on eligibility requirements to participate in the study. Participants' prior exposure to cannabis was also recorded in some studies (58%).

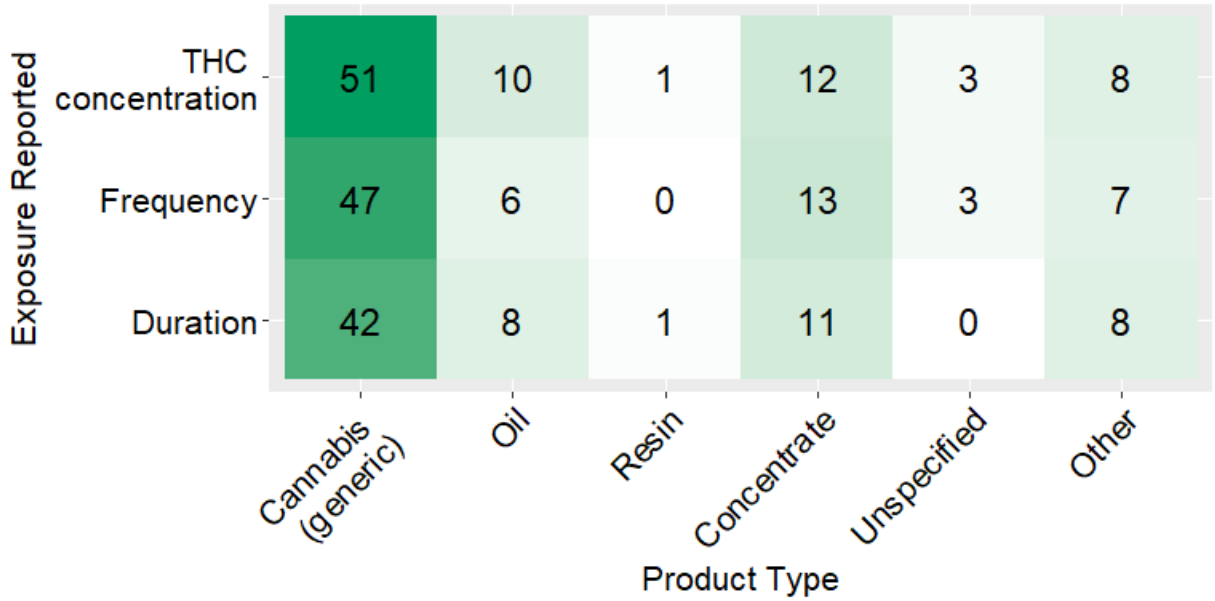
Of the studies included, funding source, author affiliations, and conflicts of interest were recorded. Information was lacking for some studies; 114 studies did not report their funding source (23%) and 189 studies did not report if authors had conflicts of interest (39%). Measures relevant to health equity were also noted, but only 67 studies included analysis on any measure of health equity (14%). Fifty-seven studies included analysis or stratification of subgroups (12%), 11 studies focused exclusively on historically excluded populations (2%), and no studies included specific analysis of structural racism or inequalities (0%).

Exposures

As of June 22, 2022, we have completed and verified data extraction for exposures and outcomes for 68 studies.[3] These studies have been extracted by a coder and reviewed by a methodologist. Cannabis products in included studies were used for medicinal (52%), recreational (24%), unintentional (4%), other (12%) purposes. Eighteen studies did not report the purpose of cannabis use (27%). Sixty-one studies reported a route of administration, including inhalation (72%), ingestion (43%), and other (34%). Fifty-seven studies (84%) reported the frequency of intake, with the most common frequency being daily (28%), and fifty-one (60%) reported the duration of intake. Cannabis exposure was reported most often in studies that included generic cannabis (Figure 4). There was a large amount of variability in reporting of THC concentration, including the units reported and the indices used (e.g., THC concentration range, threshold, exact values, mean). THC concentration was reported in percent (38%), mg (24%), mg/kg (2%), mg/ml (6%), and other units (7%). The median THC concentration for the highest THC concentration reported for each product in a study was 23% THC (IQR: 36) or 40 mg THC (IQR: 33) (Figure 5). However, no attempt was made to standardize numeric THC concentration.

[3] As of June 29, 2022, 274 studies have undergone data extraction and 43% of those studies were verified by one of the methodologists. We anticipate data extraction process to be completed by early August 2022.

Figure 4: Number of studies with reported THC concentration, frequency, and duration by cannabis product (n=68). *



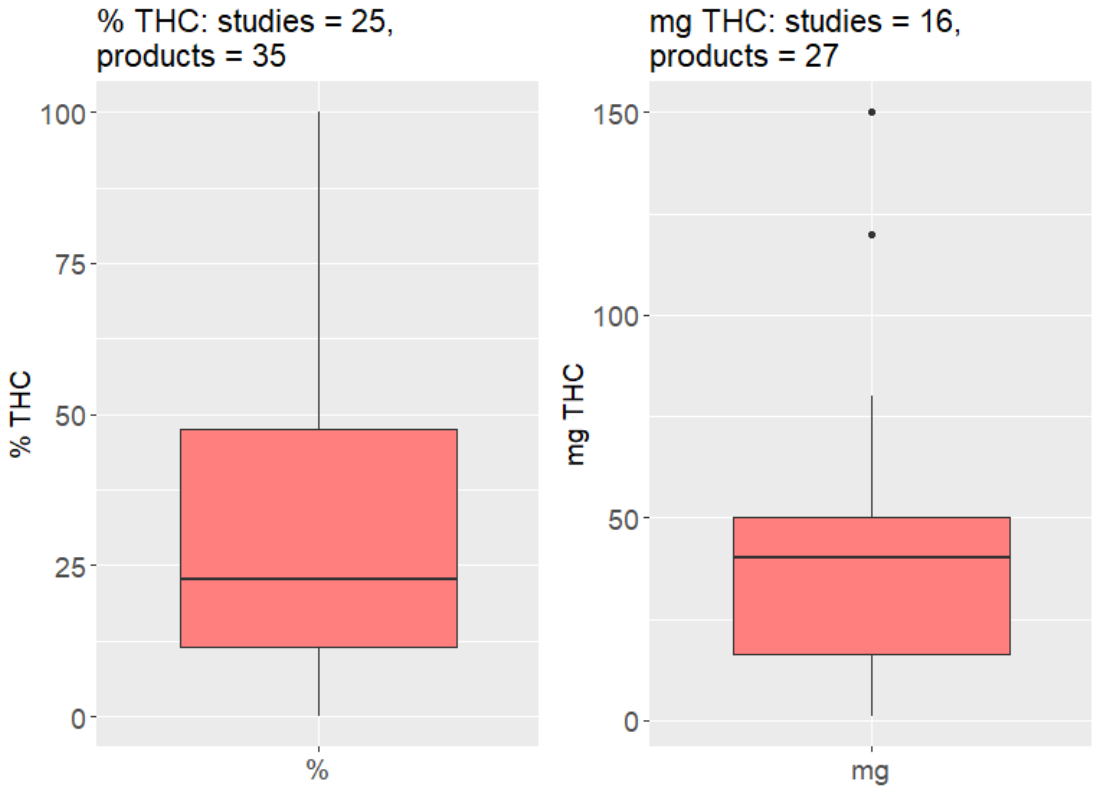
Heatmap of the number of studies by cannabis product type included in the study and cannabis exposure reported. Counts indicate the number of studies with an included cannabis product type and cannabis exposure. Studies may include multiple product types and exposures. Color saturation indicates the density of studies with a reported product/exposure in relation to other product/exposures. Products and exposures may be directly associated, indirectly associated or un-associated within each study.

*Based on data extracted through June 21, 2022.

Outcomes

The most common outcome domain for included studies was mental health (44%), followed by pain (32%), substance use /substance dependence (22%), sleep (21%), gastrointestinal (18%), neurological (18%), psychosocial (16%), cardiometabolic (9%), injury and death (4%), respiratory (4%), cancer (3%), ocular (3%), and sexual health and reproductive health (2%) (Figure 6). Twenty-nine studies (43%) reported a health outcome domain other than those listed above (the health outcome domains specified in the protocol). No outcome domain had been studied in association with all product types collected (Figure 7). The range of THC concentration studied by outcome varied widely (Figure 8). Twenty-one studies (30%) included a direct association between THC concentration and health outcomes. Eleven studies (16%) included a direct association between concentrates and health outcomes. Thirty studies (44%) included a control group. Outcomes were reported with effect estimates (52%), measures of precision (81%), significance tests (91%), sample size (97%), correlation coefficients (24%), raw data (60%), and regression coefficients (32%).

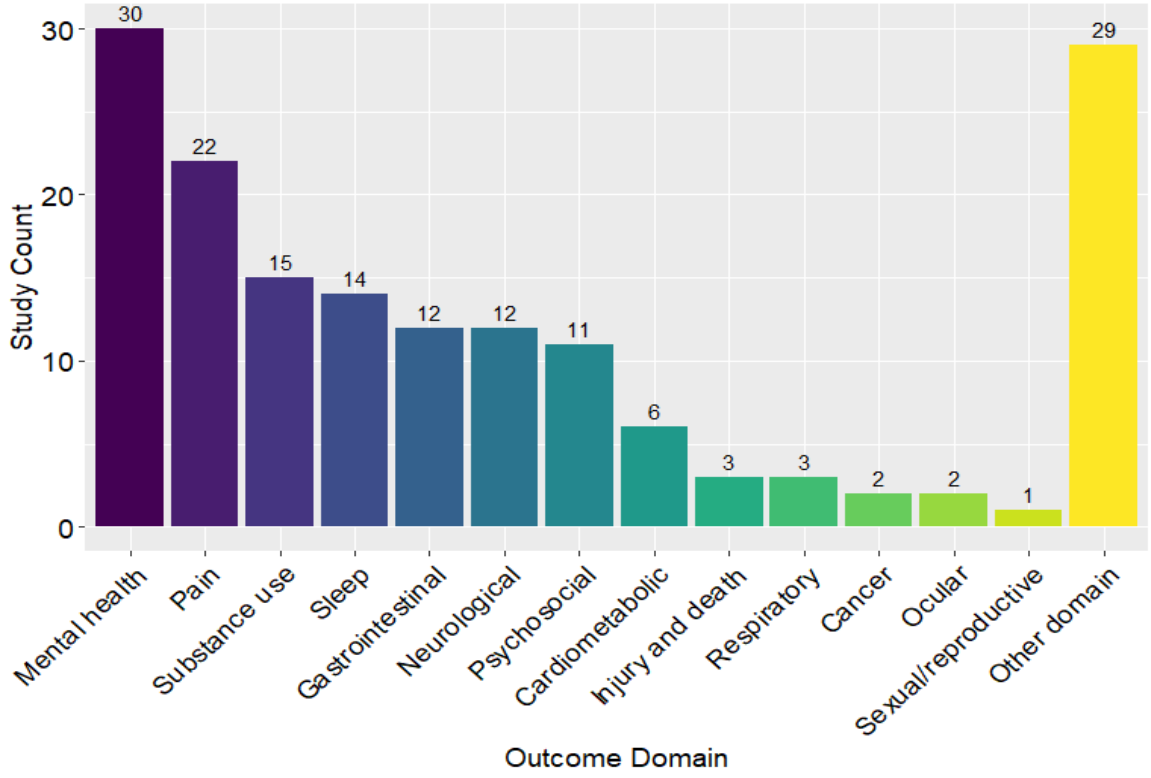
Figure 5: Highest reported THC concentration for each product in a study for THC concentration reported as % THC and mg THC (studies =42, products = 65). *



Boxplot of highest reported THC concentration by product for each study separated by units. A THC concentration was extracted for each product included in the study (e.g., edibles, dried cannabis). THC concentration may be reported as an exact concentration (e.g., 10% THC), a range (e.g., 1-10 mg THC), a threshold (e.g., <5% THC), or some other method of aggregation (e.g., mean % THC). THC concentration values were not standardized. The mid-line of the boxplot is the median THC concentration, the top and bottom of the box are fist and third quartile (Q1 and Q3), whiskers represent the Q1-1.5(IQR) and Q3+1.5(IQR), points beyond the whiskers are outliers beyond this range.

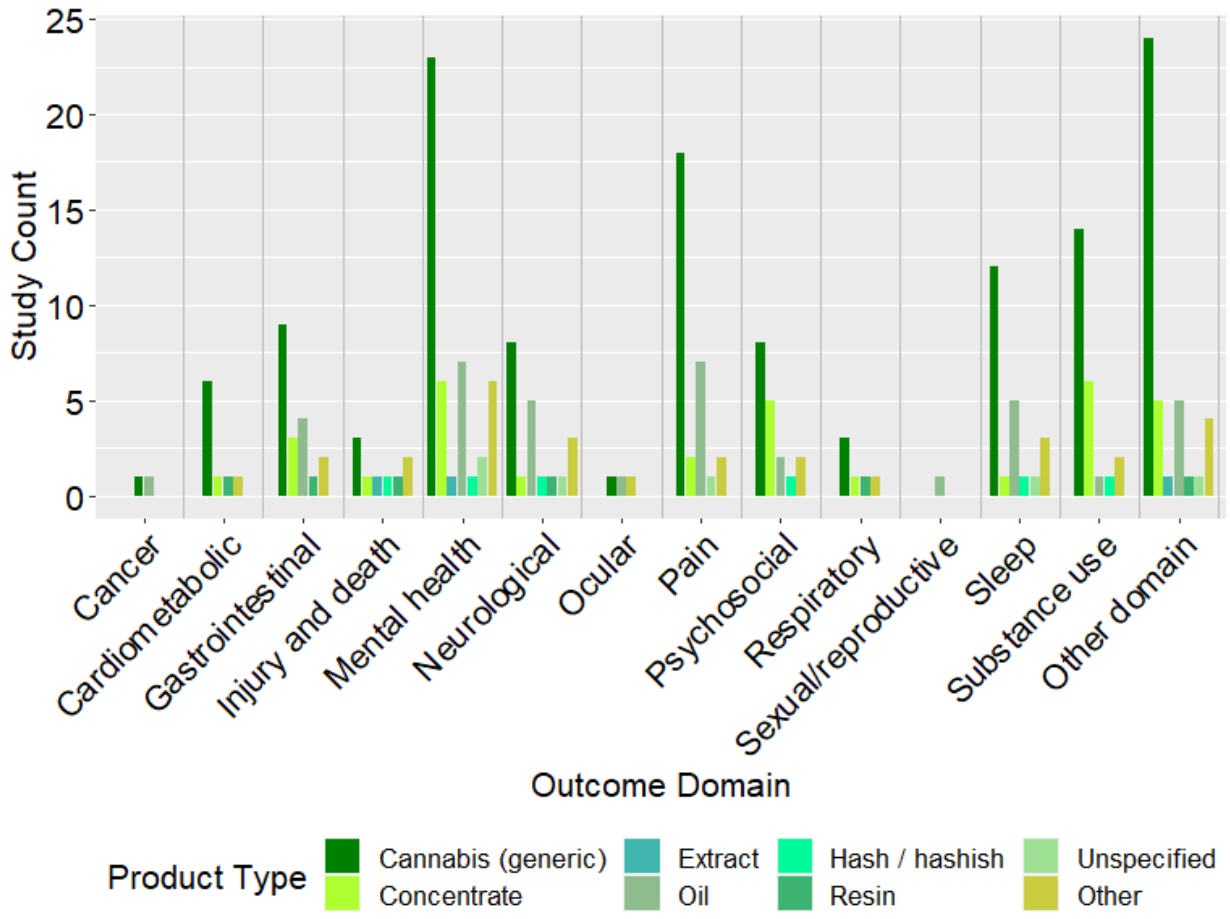
**Based on data extracted through June 21, 2022*

Figure 6: Number of studies by outcome domain reported in the study. Studies may report multiple outcome domains (n=68). *



Based on data extracted through June 21, 2022

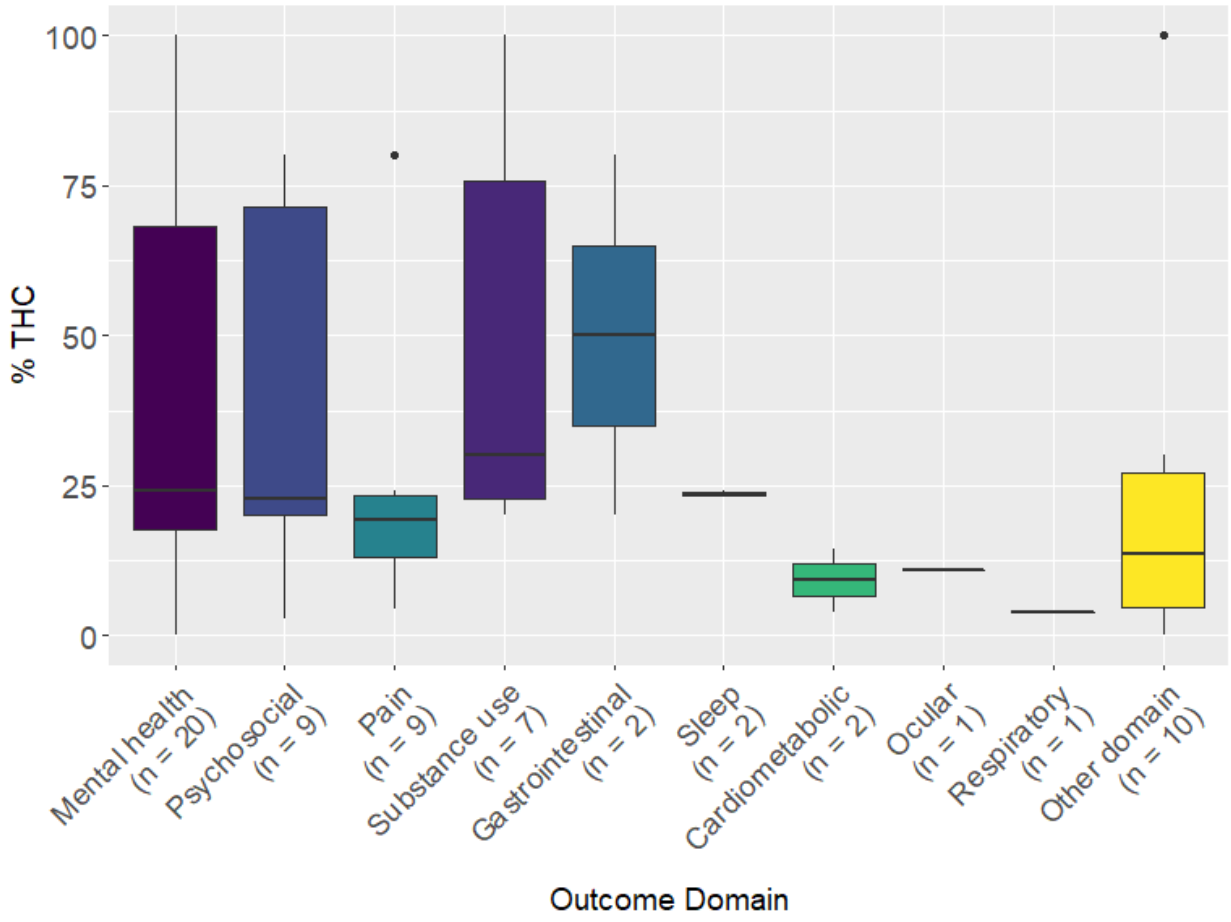
Figure 7: Number of studies by outcome domain and product type (n=68). *



Number of studies by outcome domain and cannabis product type reported in the study. Studies may report multiple outcome domains and product types.

**Based on data extracted through June 21, 2022*

Figure 8: Outcome domains of studies with THC concentration reported as % THC (studies =25, products = 35). *



Boxplot of highest reported THC concentration for concentrations reported in % THC by outcome domain. A THC concentration was extracted for each product included in the study (e.g., edibles, dried cannabis). THC concentration may be reported as an exact concentration (e.g., 10% THC), a range (e.g., 1-10 mg THC), a threshold (e.g., <5% THC), or some other method of aggregation (e.g., mean % THC). THC concentration values were not standardized. The mid-line of the box is the median THC concentration, the top and bottom of the box are fist and third quartile (Q1 and Q3), whiskers represent the Q1-1.5(IQR) and Q3+1.5(IQR), points beyond the whiskers are outliers beyond this range.

**Based on data extracted through June 21, 2022*

Discussion of Findings

We have attempted to identify all relevant and accessible literature on the effects of high-concentration THC products. To date, such a review has not been undertaken. The support for the ColoradoSPH under HB 1317 has facilitated a needed systematic review and the creation of a database that will support further work by the review team and others who will use the publicly accessible database resource. The systematic review task designated to the ColoradoSPH under HB 1317 proved to be enormous (Figure 3). The team initially identified 46,004 titles for screening and then moved through the review process to arrive at the 753 articles for data extraction. In the review process, we did not identify a similar and recent comprehensive review. The authoritative report by the Institute of Medicine was published more than five years ago in January 2017 and focused on clinical uses of cannabis (NASEM, 2017).

Our review encountered the previously identified challenges of the research literature on cannabis products and high-concentration THC products in particular. Table 6 provides some key recommendations from four prior major reports from the Institute of Medicine, CDPHE, The Washington State Prevention Research Subcommittee, and the Massachusetts Cannabis Control Commission. This is an emerging field of research for which standards are not in place for documentation of study methods and reporting of findings, a problem receiving comment in the reports of the Institute of Medicine and CDPHE (NASEM, 2017; Holdman et al., 2020). The former on the general need for public health research on THC concentrates and the latter commented on the need for improving research quality. The 2020 Washington State report also commented on the need to bring standardization to measurement (Haggerty et al., 2020). The deficiencies we noted went beyond the characterization of exposure to THC products and determinants of dose to such critical items as basic descriptors of study population characteristics and methods.

For addressing the review questions, which required identifying associations between exposures and outcomes, the review was further limited by the heterogeneity of the outcomes in the studies considered. Ideally, the review would have identified multiple studies with similarly measured outcomes, e.g., pain relief or impaired driving, and comparably measured exposures, i.e., sufficiently comparable such that exposure measures could be grouped into one common set of categories. Such groupings are needed to examine concentration-response relationships and determine how the likelihood of adverse effects or benefits depends on exposure, particularly concentration. As documented, the wide and noncomparable range of exposure categories and outcome measures poses a substantial barrier to combing the data across studies.

As noted, there have been prior authoritative reviews on harms and benefits of cannabis and THC containing products (Table 6). These are enumerated in Table 6 along with key recommendations. These reports did not give emphasis to high-concentration products.

This new review adds to the findings of these prior reports on the serious limitations of the extant scientific literature. The characteristics of the 489 studies addressed to date reflect the heterogeneity of the research, carried out in multiple venues with various funding sources. One well-known limitation is the previous requirement to use low concentration cannabis obtained from the University of Mississippi (NIDA, 2020). This material is not reflective of the current

marketplace. Overall, when THC concentration used in a study could be extracted from an article, it was below concentrations currently found in the marketplace.

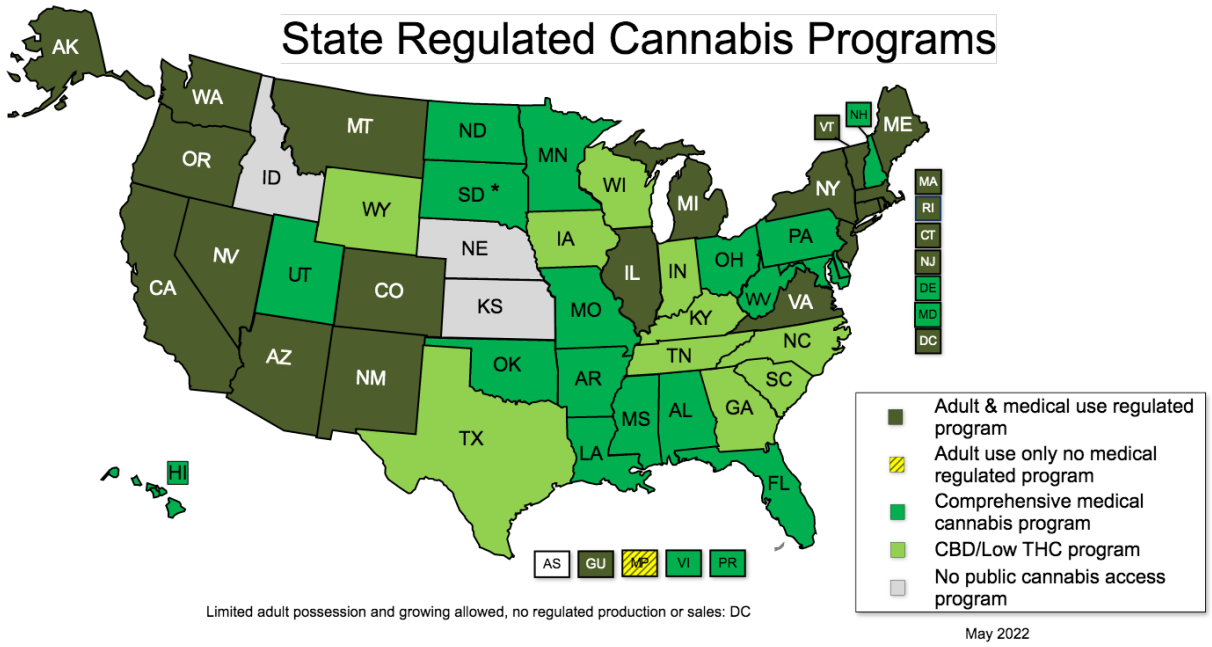
There is a pressing need for high-quality research to address the effects of high-concentration THC products (Figure 9). Colorado was the first state to legalize non-medical use of cannabis. As of February 3, 2022, 37 states, four territories and the District of Columbia permit cannabis products for medical use. A total of 19 states, two territories and the District of Columbia have authorized the regulation of cannabis products for non-medical use by adults. Undoubtedly, legal access to cannabis products will increase. Surveillance data for Colorado are informative on the extent of use of cannabis products.

Colorado has robust public health surveillance systems, including population-based surveys of adults and youth (the Behavioral Risk Factor Surveillance System (BRFSS), and the Healthy Kids Colorado Survey (HKCS), both conducted by the Colorado Department of Public Health and Environment. Data from these surveys are available from prior to legalization of recreational marijuana, allowing an understanding of trends in marijuana use behaviors in Colorado.

The state prevalence of current (past month) marijuana use among adults 18 and older is estimated to be 18.9%, according to the most recent administration of the BRFSS in 2020. Colorado has consistently had a higher prevalence of use than the national average, but a similar trend of slowly increasing prevalence of use. The most common mode of use continues to be smoking marijuana, with 73.9% of adults who currently use marijuana reporting smoking marijuana in the past 30 days. However, a sizable proportion report other methods of use including 43.1% who ate or drank marijuana, 21.7% vaporized, 17.4% dabbed, and 4.4% used it in some other way (not mutually exclusive). Modes other than smoking most likely represent the use of a concentrated product, and smoked flower may include high percent THC flower. There are not clear trends in the change in mode of marijuana use other than a slow decline in the proportion that smoke marijuana and an increase in all other modes of use, between 2015 and 2020.

In the most recent administration of the HKCS, in the fall of 2021, the prevalence of current use (past 30 day) of marijuana among high school students was 13.3%. This is a decline to the prevalence prior to the COVID-19 pandemic, which was 20.6% in the fall of 2019. Among the high school students who reported current marijuana use, half (50%) reported they usually smoked it, with the remaining students responding that the most common mode of use was a mode other than smoking it (e.g., ate, dabbed, or vaped). Among the high school students who reported current marijuana use, students report multiple modes of use: 79.5% smoked marijuana, 49.2% dabbed, 39.1% vaped, 36.6% ate it (edibles), and 10.3% reported using it in other ways (not mutually exclusive).

Figure 9: Overview of distribution of regulated cannabis programs throughout the United States. A total of 37 states, four territories and the District of Columbia permit cannabis products for medical use as February 3, 2022. While 19 states, two territories and the District of Columbia have authorized the regulation of cannabis products for non-medical use in adults (NCSL, 2022).



Next Steps

As this report is written, the ColoradoSPH team is moving towards completion of data extraction from the 489 studies with information on exposures and outcomes. With completion of data extraction during July 2022, next steps will utilize the evidence map to:

- Examine the exposure/outcome pairs and assess the availability of data relevant to the review's main questions;
- Determine if there is sufficient evidence to warrant focused systematic reviews that would address high-concentration THC products;
- Characterize critical research gaps.

A subsequent step in meeting the mandate of HB 1317 would be to carry out focused systematic reviews for exposure/outcome pairs with sufficiently robust data. For these reviews, protocols for carrying out a systematic review would be followed, including the specification of a study question and assessment of the quality of studies, and then proceeding through the steps of a systematic review (Figure 1). Depending on the scope of the data and its characteristics, the data might be pooled via a meta-analysis and dose-response relationships might be modeled.

We plan a follow-up report to be submitted in September 2022 after data extraction is complete and the findings from the resulting database have been fully assessed. That report will set out a complete roadmap for next steps in the review process including the anticipated products and the schedule for submitting them to the legislature. We recognize that submission in advance of the 2023 General Assembly is needed. We anticipate making recommendations in the follow-up report that will suggest directions for future research and for improving the quality of research. We will work in tandem with the Scientific Review Council.

Table 1: Cannabis Research & Policy Project Team Members

Member	**Sub-Team**
Lisa Bero, PhD	Systematic Review
Ashley Brooks-Russell, PhD, MPH	Subject Area Expertise
Meghan Buran, MPH	Administration
Rosa Lawrence, BA	Systematic Review
Louis Leslie, BA	Systematic Review
Tianjing Li, MD, PhD, MHS	Systematic Review
Jean-Pierre Oberste, BA	Systematic Review
Christi Piper, MLIS	Systematic Review
Thanitsara Rittiphairoj, MD, MPH	Systematic Review
Jonathan Samet, MD, MS	Administration
Neeloofar Soleimanpour, MPH	Administration
Gregory Tung, PhD, MPH	Administration, Subject Area Expertise
G. Sam Wang, MD	Subject Area Expertise

Table 2: Scientific Review Committee Members

Member	Role on Council per HB 1317	Affiliation(s)
Chris Urbina, MD, MPH (Chair)	Preventive medicine specialist (or preventive medicine public health professional)	Pueblo Department of Public Health and Environment; Former Director of CDPHE
Gregory Kinney, PhD, MPH	Epidemiologist	Colorado School of Public Health
David Brumbaugh, MD, MSc	Physician familiar with the administration of medical marijuana pursuant to current state laws to those aged zero to seventeen	Children's Hospital Colorado; University of Colorado School of Medicine
Kennon Heard, MD	Medical Toxicologist	University of Colorado School of Medicine
Archana Shrestha, MD	Neurologist	University of Colorado School of Medicine
Erica Wymore, MD, MPH	Pediatrician	University of Colorado, School of Medicine
Paula Riggs, MD	Psychiatrist	University of Colorado, School of Medicine
Susan Calcaterra, MD, MPH	Internal medicine physician (or other specialist in adult medicine)	University of Colorado School of Medicine
Joseph Schacht, PhD	Licensed Substance Abuse Disorder Specialist	University of Colorado School of Medicine
Kent Hutchison, PhD	Neuropsychopharmacologist	University of Colorado School of Medicine
Lesley Brooks, MD	Medical professional (or public health professional) who specializes in racial and health disparities and systemic inequalities in health care and medicine	North Colorado Health Alliance; SummitStone Health Partners

Table 3: Examples of health outcomes studied for high-concentration THC cannabis products and concentrates.

Outcome Category	Examples
Cancer	Management of glioma tumor; occurrence of testicular germ cell tumors
Pain	Chronic pain in adults, palliative care
Psychosocial	Social anxiety, quality of life, academic achievement, employment and income, social relationships and other social roles
Mental Health	Anxiety, depressive symptoms, posttraumatic stress disorder (PTSD), schizophrenia and other psychoses, bipolar disorder, depression, suicide, and psychosocial distress
Substance Use / Substance Dependence	Treatment for addictive substance use, such as for opioid dependence. Occurrence of alcohol, tobacco, opioid, and cannabis use disorders
Cardiometabolic	Acute myocardial infarction, stroke, metabolic dysregulation, diabetes, and hypertension
Respiratory	Pulmonary function, COPD, respiratory symptoms including chronic bronchitis, and asthma
Immunity	Immune competence, susceptibility, and progression of infectious disease
Pre-, Peri-, and Neonatal	Pregnancy complications, fetal growth and development, neonatal conditions, and later developmental outcomes
Gastrointestinal	Treatment for chemotherapy-associated nausea and vomiting, HIV/AIDS associated anorexia and weight loss, cancer-associated anorexia-cachexia, anorexia nervosa, symptoms of irritable bowel syndrome, hyperemesis
Neurological	Dyskinesia, dementia, epilepsy, spasticity associated with multiple sclerosis or spinal cord injury, symptoms associated with Tourette syndrome, motor and cognitive symptoms of Huntington's disease, Amyotrophic Lateral Sclerosis, and Parkinson's disease, levodopa-induced dyskinesia, dementia, mortality, and disability associated with traumatic brain injury or intracranial hemorrhage
Ocular	Reduction in glaucoma intraocular pressure
Sleep	Sleep disturbances, sleep quality
Injury and Death	Decreased mortality associated with traumatic brain injury, intracranial hemorrhage. All-cause mortality, occupational injury, motor vehicle crashes

Table 4: Condensed list of data extraction elements.

Domain	Data Item
Study Characteristics – Main Form	
Bibliographic Information	Author information, and conflict of interest and funding statement
General Study Details	Study objectives, study design, restrictions on eligibility criteria related to health conditions
Study Population	Number of study participants, country, sex, race, ethnicity, and age/developmental stage
Others	Exposure history and information related to health equity
Exposure and Outcomes – Main Form	
Exposure Type	Type of cannabis product, purpose of cannabis use, and route of administration
Exposure Concentration	THC concentration range, biomarker reported, non-THC cannabinoids components, and frequency and duration of intake
Outcome	Health outcome domains, exposure-outcome association, and information related to quantitative data and analyses

Table 5: Summary of study characteristics (n = 489).

Category	n	%
Author affiliations for any author by study		
Academic	437	86.7
Government	96	19.0
Commercial/private	66	13.1
Non-governmental organization/non-profit	27	5.4
Other	19	3.8
Not reported	14	2.8
Conflict of interest of any author by study		
States authors have no conflicts	234	46.4
Pharmaceutical Industry	61	12.1
Cannabis Industry	52	10.3
Government	28	5.6
Non-governmental organization/non-profit	16	3.2
Other	20	4.0
Not reported	201	39.9
Study funding		
Government	252	50.0
Non-governmental organization/non-profit	68	13.5
States there was no funding for the study	39	7.7
Pharmaceutical Industry	22	4.4
Cannabis Industry	19	3.8
Other	61	12.1
Not reported	118	23.4
Study design		
Observational/epidemiological	300	59.5
Randomized controlled trial	188	37.3
Unclear	6	1.2
Other	4	0.8
Not reported	6	1.2
Overall study objectives		
Harm only	229	45.4
Both	157	31.2
Efficacy only	118	23.4
Restrictions on eligibility criteria of study population		

Category	n	%
Healthy	175	34.7
Pain	66	13.1
Neurologic	50	9.9
Oncologic	50	9.9
Psychiatric	42	8.3
Gastrointestinal	19	3.8
Infection	7	1.4
Pulmonary	7	1.4
Ophthalmological	5	1.0
Alcohol/opioid use disorder	5	1.0
Cardiovascular	4	0.8
Diabetes	2	0.4
Other	82	16.3
Not reported	66	13.1
Analyzed indicators of health equity		
No	430	85.3
Yes	69	13.7
Unclear	5	1.0
Included health equity subgroup analysis or stratification		
No	443	87.9
Yes	59	11.7
Unclear	2	0.4
Analyzed structural racism or inequalities		
No	502	99.6
Unclear	2	0.4
Yes	0	0.0
Focused exclusively on historically excluded populations		
No	492	97.6
Yes	11	2.2
Unclear	1	0.2
Participant recruitment by country (3 most frequent countries listed)		
United States of America (US)	236	46.8
United Kingdom (UK)	56	11.1
Canada	54	10.7
Other	173	34.3

Category	n	%
Not reported	20	4.0
Participant recruitment by state (3 most frequent states listed)		
California	55	10.9
Colorado	28	5.6
New York	20	4.0
Other	215	42.7
Sex		
Male	438	86.9
Female	389	77.2
Transgender	5	1.0
Non-Binary	1	0.2
Other	12	2.4
Not reported	36	7.1
Race		
White	155	30.8
Black or African American	98	19.4
Asian	59	11.7
Multiracial	27	5.4
American Indian or Alaskan Native	25	5.0
Native Hawaiian or Pacific Islander	14	2.8
Other	84	16.7
Not reported	342	67.9
Ethnicity		
Hispanic or Latino	79	15.7
Not Hispanic or Latino	40	7.9
Other	17	3.4
Not reported	415	82.3
Age/developmental stage		
Adult (25-64)	369	73.2
Young adult (18-24)	307	60.9
Older adult (65 and over)	155	30.8
Adolescent (9-17)	66	13.1
Child (1-8)	24	4.8
Birth to <1 years of age	14	2.8
Pregnancy	4	0.8

Category	n	%
Preconception	1	0.2
Postpartum maternal	1	0.2
Postpartum breastfeeding	1	0.2
In utero	0	0.0
Other	51	10.1
Not reported	47	9.3
Exposure to cannabis prior to study observations		
Chronic	59	11.7
Acute	24	4.8
No use in previous year	11	2.2
Other	172	34.1
Not reported	217	43.1

Table 6: Direct quotes from previously published authoritative reviews on systematic reviews and harms and benefits of cannabis and THC containing products from the Institute of Medicine, CDPHE, the Washington State Prevention Research Subcommittee, and the Massachusetts Cannabis Control Commission along with their key recommendations respectively (NASEM, 2017; Holdman et al., 2020; Haggerty et al., 2020, Doonan et al., 2021).

Report Name:	Key Recommendations:
1. Institute of Medicine, January 2017	• "Unfortunately, the literature remains unclear on the association or developmental link between varying levels of cannabis use and the development of "problem" cannabis use or cannabis use disorder, particularly at different age groups (e.g., 12 years or older)." • "There is substantial evidence for a statistical association between increases in cannabis use frequency and the progression to developing problem cannabis use." • "There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research." • "It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use." • "A diverse network of funders is needed to support cannabis and cannabinoid research that explores the harmful and beneficial health effects of cannabis use." • "To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed."
2. Colorado Department of Public Health and Environment, July 2020	• "Increase awareness, education and understanding of THC concentration." • "Increase adult consumer awareness and education about the risks of mental health effects from using marijuana products with high THC concentration." • "Encourage use of the term THC concentration in place of potency." • "Monitor rates of adverse events stratified by product type." • "Monitor THC concentration among marijuana products available on the regulated retail market in Colorado." • "In Colorado, almost all retail marijuana products contain high THC concentration, rarely containing less than 10% THC. Evidence is moderate to strong concerning THC

	concentration and the association with mental health effects in adolescents, young adults and adults. When examining specific types of marijuana products and the impact on blood THC levels, the evidence is strong for marijuana flower, moderate for both edibles and vaporized products and limited for THC concentrate products."
3. Washington State Prevention Research Subcommittee, November 2020	• "Research available to date documents that THC content in cannabis products contributes to adverse health effects in a dose-response manner. This increased risk imposed from using higher potency cannabis products is particularly concerning for young users and those with certain pre-existing mental health conditions. To further our understanding on the impact of high-THC content cannabis products, more research is needed." • "People who report low socio-economic status, being of Latinx descent, and poor mental health are more likely do dab in Washington." • "Manufactured cannabis products such as high potency concentrates are more likely to contain residues and contaminants due to the extra steps needed for their production, including solvent-base extraction and additives. The health effects of exposing human lungs to possible residues are still not fully known." • "Poison Centers nationally are receiving more calls about manufactured cannabis products including edibles, concentrates, and vaping liquids. Manufactured products are more likely than plant products to be the only substance involved in the case. Children may be at greater risk for exposure. More serious health outcomes were observed for vape liquid exposures during late 2019, possibly associated with the vape-related EVALI outbreak during this time" • "No consensus has been achieved on the relationship between THC blood levels and levels of impairment. As such, there is a great need for additional research on THC concentration and driving performance."
4. Massachusetts Cannabis Control Commission, October 2021	• **"**Commission staff find that evidence is not sufficient to recommend a specific concentration cap at this time." • "As a result of the gaps in the research, we do not draw a conclusion regarding the effects of high-THC medical cannabis on the human body." • "Instead, staff offer considerations to increase research capacity for evidence-based decisions regarding THC limits in the future. Non-medical use of high THC

products and greater doses of cannabis products by some populations appear associated with greater health and public safety risks than lower dose use; however, additional research is needed."

- "Based on current finding, THC use presents some health risks for youth, and risks appear greater for youth using high-THC cannabis products."
- "A reassessment may be warranted as the scientific evidence basis matures in the future as additional research is conducted."
- "Researchers and clinicians could develop guidelines on how to administer medical cannabis of varying concentration, including indicators of potential side effects, and effectiveness for specified conditions. It is also important to consider the labeling and packaging of products to ensure that patients understand the concentration dosage of their prescription. This would assist medical providers to be able to guide patients in more safe and effective ways to consume cannabis for medicinal treatment."
- "Research shows that most cannabis consumers do not fully understand labeling and what constitutes high THC concentration products. To increase understanding, the Commission could create additional public awareness materials or build upon its campaign, "More About Marijuana," to educate consumers on what constitutes high-THC concentration cannabis."

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