A Scoping Review on Health Effects of High-Concentration Cannabis Products: Findings on Key Policy Questions

April 19, 2023

Cannabis Research and Policy Project Team

Colorado School of Public Health

The University of Colorado Anschutz Medical Campus

Contact:

Jonathan M. Samet, MD, MS

Dean, Colorado School of Public Health

cannabis.research@cuanschutz.edu

Submitted to:

House Finance and Public and Behavioral Health and Human Services Committees

And

Senate Finance and Health and Human Services Committees

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Introduction

Under Colorado House Bill 21-1317 (HB 1317) (CONCERNING THE REGULATION OF MARIJUANA FOR SAFE CONSUMPTION, AND, IN CONNECTION THEREWITH, MAKING AN APPROPRIATION) the Colorado School of Public Health (ColoradoSPH) was mandated to carry out a systematic review "…related to the physical and mental health effects of high-potency [*Note added: Delta-9-Tetrahydrocannabinol (THC)*] THC marijuana and concentrates." Additionally, HB 1317 required that the ColoradoSPH "…shall produce a public education campaign for the general public regarding the effect of high-potency marijuana on the developing brain and on physical and mental health." The ColoradoSPH was also charged with establishing the Scientific Review Council (Appendix Table 1) for which the members were mandated in the bill. While the language of HB 1317 refers to "high-potency" marijuana, we use the term "high-concentration" in this report as it is more appropriate scientifically.

Note: We offer the reminder that this is a focused review on questions related to the charge given to the ColoradoSPH by HB 1317. It is not a general review of the broad scope of issues related to public health and to beneficial/medical uses of cannabis and THC. Rather, the focus is "…on physical and mental health effects of **high-potency** THC marijuana and concentrates," per the charge to the ColoradoSPH. For those seeking information on marijuana and concentrates generally, there are general resources available, such as the CDC's Marijuana and Public Health page and NIDA's Cannabis (Marijuana) DrugFacts page. This report and the scope of our work under the charge of HB 1317 do not address cannabinoids other than THC.

At this point in filling the charge under HB 1317, the ColoradoSPH team has completed the scoping review including all studies informative on high-concentration products published by November 19, 2022. A Tableau dashboard has been implemented and an evidence map created so that the 452 studies meeting criteria can be filtered and utilized to address the charge given to the ColoradoSPH by the Colorado General Assembly.

This report describes findings based on the evidence map relevant to the four Policy Questions (Table ES-1) developed using the intent of HB 1317 as the starting point with input from the Scientific Review Council. For each question, all studies available were reviewed and a narrative summary of the evidence prepared. This report provides a qualitative summary of the relevant evidence and conclusions on the availability of evidence relevant to each of the questions. The report also provides an update on the status of the development of the educational campaign.

Table ES-1: Policy Questions evaluated based on the evidence map.

The Four Policy Questions
1. Are adolescents and young adults especially susceptible to adverse physical or mental health outcomes of high-concentration cannabis products?
2. Are individuals with preexisting mental health conditions especially susceptible to adverse mental health outcomes of high-concentration cannabis products?
3. Are pregnant and nursing women susceptible to adverse physical or mental health outcomes of high-concentration cannabis products? Are infants/children with prenatal and postnatal exposure to high-concentration cannabis products susceptible to adverse physical, neurodevelopmental or cognitive effects from this exposure?
4. Are high-concentration THC cannabis products associated with greater risk of adverse physical or mental health outcomes than lower-concentration products?

Methods

Using the evidence map, we identified all studies relevant to each of the four Policy Questions and prepared a narrative summary. We evaluated the evidence as recommended in the Synthesis without Meta-Analysis Guidelines and developed a qualitative synthesis of a very heterogeneous body of evidence for each of the four questions. We counted the number of studies with statistically significant associations for an adverse or a beneficial effect and the number of studies with associations that are not statistically significant. Statistical significance is a determination that the association between two factors is likely caused by something other than chance. The number of such studies without statistical tests is noted.

Using statistical significance, we classified studies relating to Policy Questions 2 and 4 as showing (1) a significant association, (2) a non-statistically significant association, or (3) not assessed (frequency, duration, and mg/% THC). A study was classified as showing an "effect" if it found at least one statistically significant association with the outcome of interest in the study's final analysis. A study was classified as having "no effect" if the study conducted a final statistical test or test but none of the tests of association were statistically significant. Finally, a study was classified as "not assessed" if the report only provided descriptive statistics without testing statistical significance of associations.

Also, during full-text review, team members characterized the findings for the outcomes as 'beneficial' or 'adverse' for each study, using the study's definitions of adverse or beneficial findings. Last, for each Policy Question and outcome domain, we applied a classification for the amount of available evidence based on the number of statistically significant studies. Study numbers are classified as: none, limited (1-4), moderate (5-9), and substantial (10+).

Results

The overall findings for each of the four Policy Questions are summarized in Table ES-2, which provides the results of the review, stratified by whether the outcome was considered adverse or beneficial. The table highlights the range of outcomes covered by the evidence map and the limited availability of studies addressing the four Policy Questions (Table ES-2).

Pharmacokinetic Considerations

In reaching overall conclusions based on the scientific literature identified for the four Policy Questions, we also considered the determinants of how much THC reaches receptors in the brain. The modality of use (inhalation, ingestion) and the characteristics of the product (%/mg THC) and users (e.g., age, preexisting health conditions) are key determinants influencing the exposure dose of the effect of THC that is absorbed and the effect on an individual. Like other ingested and inhaled substances, THC is distributed throughout the body and undergoes metabolism; thus, factors affecting distribution and metabolism affect the THC dose that reaches brain receptors. An individual's tolerance is also critical; the more tolerant an individual is, the more THC is needed to achieve the same pharmacological effect. Individual health characteristics include age of initiation or use, preexisting health conditions, and genetic make-up also affect the response to THC. These considerations related to the THC dose reaching the brain suggest that limiting concentration levels in cannabis products alone will not prevent harmful THC levels from reaching the brain.

Conclusions

Table ES-2: Conclusions by Policy Question and Outcome Domain.

Policy Question	Outcome Domain	Number of Statistically Significant Studies	Evidence Scope on Adverse Effects	Evidence Scope on Beneficial Effects
1. Are adolescents and young adults especially susceptible to adverse physical or mental health outcomes of high-concentration cannabis products?	Mental Health Conditions and Substance Use	2	**Limited** Amount of Evidence	-

2. Are individuals with preexisting mental health conditions especially susceptible to adverse mental health outcomes of high-concentration cannabis products?	Adverse Mental Health Outcomes	2	**Limited** Amount of Evidence	-
	Beneficial Applications for Mental Health Conditions	6	-	**Moderate** Amount of Evidence
3. Are pregnant and nursing women susceptible to adverse physical or mental health outcomes of high-concentration cannabis products? Are infants/children with prenatal and postnatal exposure to high-concentration cannabis products susceptible to adverse physical, neurodevelopmental or cognitive effects from this exposure?	Pre-, Peri-, and Neonatal	0	-	-
4. Are high-concentration THC cannabis products associated with greater risk of adverse physical or mental health outcomes than lower-concentration products? *	Cancer Symptom Management	1	**Limited** Amount of Evidence	-
	Driving Performance	3	**Limited** Amount of Evidence	-
	Mental Health	8	**Moderate** Amount of Evidence	-
		4	-	**Limited** Amount of Evidence
	Neurologic	1	**Limited** Amount of Evidence	-

			1	-	**Limited** Amount of Evidence
	Pain		2	-	**Limited** Amount of Evidence
	Per-, Peri-, and Neonatal		0	-	-
	Pregnancy		0	-	-
	Psychosocial		1	**Limited** Amount of Evidence	-
	Sleep		1	**Limited** Amount of Evidence	-
			2	-	**Limited** Amount of Evidence
	Substance Use / Substance Dependence		1	**Limited** Amount of Evidence	-
	Other	Dry Mouth	1	**Limited** Amount of Evidence	-
		Perceived Health	2	-	**Limited** Amount of Evidence

Note: To capture the scope of the evidence, a scale was created for the amount of the available evidence based on the number of statistically significant studies. The numbers of studies are classified as: none, limited (1-4), moderate (5-9), and substantial (10+).

***** In reference to policy-question four, the following outcome domains: cardiometabolic (n=3), gastrointestinal (n=1), immunity (n=1), ocular (n=1), respiratory (n=2), and sexual and reproductive health effects (n=1) did not provide sufficient data to rate conclusions because either no statistical tests were performed, or no statistical associations were found.

Overarching Conclusions

- From the outset of this review, the scientific research focusing on high-concentration cannabis was found to be limited, particularly in its relevance to the products available today. Limitations in research methods reflect the practical difficulties in doing research on cannabis because of restricted funding, lack of standardized methods for assessing

exposure, and the wide range of outcomes studied using experimental and observational approaches. Additionally, the cannabis available for research purposes in the United States had a far lower THC concentration than that consumed. The generalizability of the accumulated scientific evidence is critically limited for addressing questions about today's marketplace.

- As to Policy Question 4, whether high-concentration products pose a greater risk for adverse outcomes, there is evidence for mental and behavioral health outcomes. We did conclude that there is a **Moderate Amount of Evidence** (eight statistically significant studies of 19 total studies) that high-concentration THC cannabis products are associated with adverse mental health outcomes for those with preexisting mental health conditions.

- As to Policy Question 2, there was evidence that high-concentration THC cannabis products have been associated with beneficial outcomes in those with pre-existing mental health conditions. We found that there is **Moderate Amount of Evidence** (six statistically significant studies of 15 total studies) that high-concentration THC cannabis products are associated with beneficial outcomes for those with a range of preexisting mental health conditions. However, for any of the specific outcomes within the broad category of mental health outcomes, the number of studies was limited.
- The evidence reviewed does not provide an accurate picture of how risk for adverse outcomes varies with concentration or other indicators of THC dose. That is, the literature is not sufficiently robust to determine, for example, if risks increase only above some threshold level of concentration (or dose) or increase with increasing concentration without a threshold. Considering the wide range of products and patterns of use, the pharmacokinetics of THC and the phenomenon of tolerance, there is not a strong basis for anticipating that thresholds can be identified for THC concentration that might be useful for informing product safety standards.

Limitations

Under HB 1317, the ColoradoSPH was given a specific charge related to high-concentration marijuana and THC concentrates. The review was targeted by design to that question. Thus, we did not review the full range of concentrations on cannabis use. The review by the ColoradoSPH did not have the purpose of reaching any conclusions on the broad impact of legalized access to cannabis and THC-containing products for recreational purposes.

The approach taken has inherent limitations, particularly when compared with carrying out multiple full systematic reviews. We have not yet completed full risk of bias assessments (i.e., assessment of internal validity) as would be done in a systematic review. The approach followed for synthesis—counting the number of studies available and tallying findings of those doing statistical significance testing—has limitations as well. Thus, the summary is qualitative and does not provide any information on the magnitude of effect, does not account for differences in

study size or risk of bias. Considering statistical significance as a criterion can exclude studies that are underpowered, i.e., not large enough, to detect a clinically important effect.

Reviewing the summaries, the limitations of the available evidence are clear. One critical problem for many of the outcomes is the limited scope of literature available. The evidence is classified as **Moderate Amount** for only two of the outcomes while the rest are **Limited Amount** or completely lacking relevant studies. For some outcomes with the most abundant evidence, e.g., mental health, the diversity of outcomes investigated poses a barrier to reaching certain conclusions.

Recommendations

- Some of the problems of the scientific literature on cannabis have been recognized; they need to be addressed so that future research is more informative. In particular, standardized approaches are needed for characterizing the use of cannabis products to assure comparability among studies. These approaches need to be modified in a timely way so that the instruments used for research reflect current patterns of use. Systematic reviews and meta-analyses would be facilitated by such standardization. Attention to use of common methods for outcome assessment in studies of cannabis would be similarly valuable.
- We are preparing a commentary on these problems for publication in the scientific literature. Advances in methodology could be made by convening researchers and research funders to develop standardized approaches, as done for other environmental agents, e.g., tobacco products.
- Following input from the Scientific Review Council, we plan to complete systematic reviews related to mental health outcomes.
- With funding from the State of Colorado, a valuable resource that will be publicly available has been developed for public health and scientific purposes. To our knowledge, the scoping review and evidence map are unique. We recommend sustained support to continually update this resource, given the rapid growth of the scientific literature, the growing availability of recreational and medical cannabis, and the availability of high-concentration products.

INTRODUCTION

Under Colorado House Bill 21-1317 (HB 1317) (CONCERNING THE REGULATION OF MARIJUANA FOR SAFE CONSUMPTION, AND, IN CONNECTION THEREWITH, MAKING AN APPROPRIATION) the Colorado School of Public Health (ColoradoSPH) was mandated to carry out a systematic review "…related to the physical and mental health effects of high-potency [*Note added: Delta-9-Tetrahydrocannabinol (THC)*] THC marijuana and concentrates." Additionally, HB 1317 required that the ColoradoSPH "…shall produce a public education campaign for the general public regarding the effect of high-potency marijuana on the developing brain and on physical and mental health." The ColoradoSPH was also charged with establishing the Scientific Review Council (Appendix Table 1) for which the members were mandated in the bill. While the language of HB 1317 refers to "high-potency" marijuana, we use the term "high-concentration" in this report as it is more appropriate, scientifically.

For context, Figures 1 and 2 provide the THC concentrations for marijuana flower and THC concentrates starting from 2014 —the year that recreational cannabis became legally available in Colorado— through 2020. Since 2014, the rise in THC concentration in both flower and concentrate products is evident: from below 15% to 20% in flower (Figure 1) and from 40 to 70% in concentrates (Figure 2). While data prior to 2014 are not available for Colorado, the THC concentration of cannabis seized by the Drug Enforcement Agency increased from less than 5% to over 16% from 1995 through 2021.[1] These data are relevant to interpreting the studies considered in this review, which span from prior decades with relatively low THC concentrations to those in the current marketplace.

Figure 1: Average THC content (%) per gram of flower based on the data published by the Colorado Department of Revenue 2020 Marijuana Market Update Report.[2]

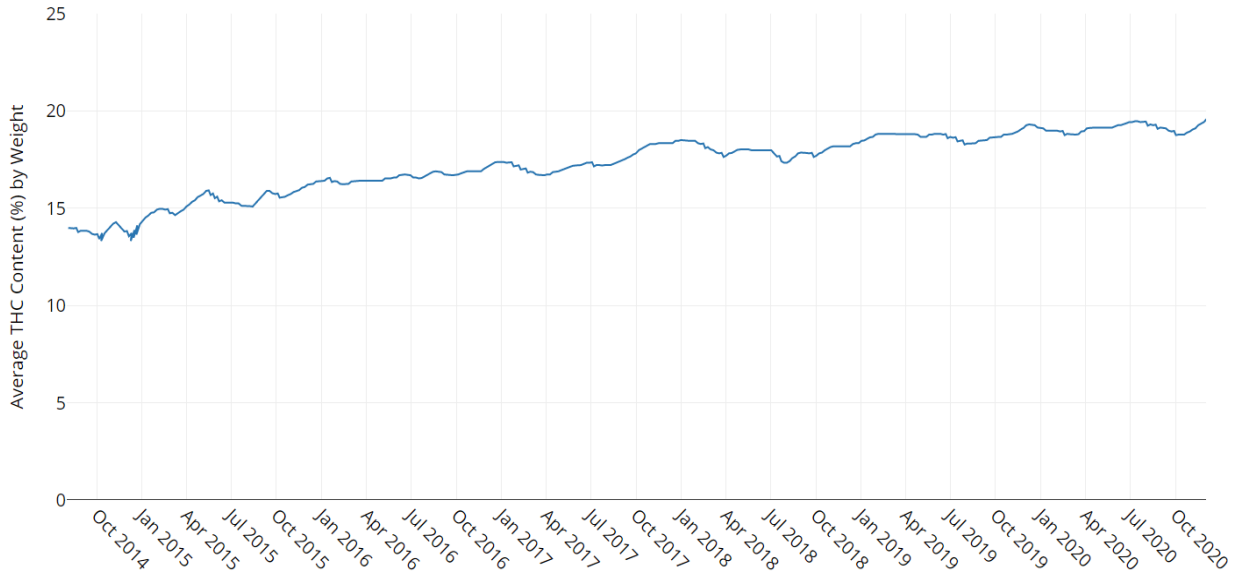
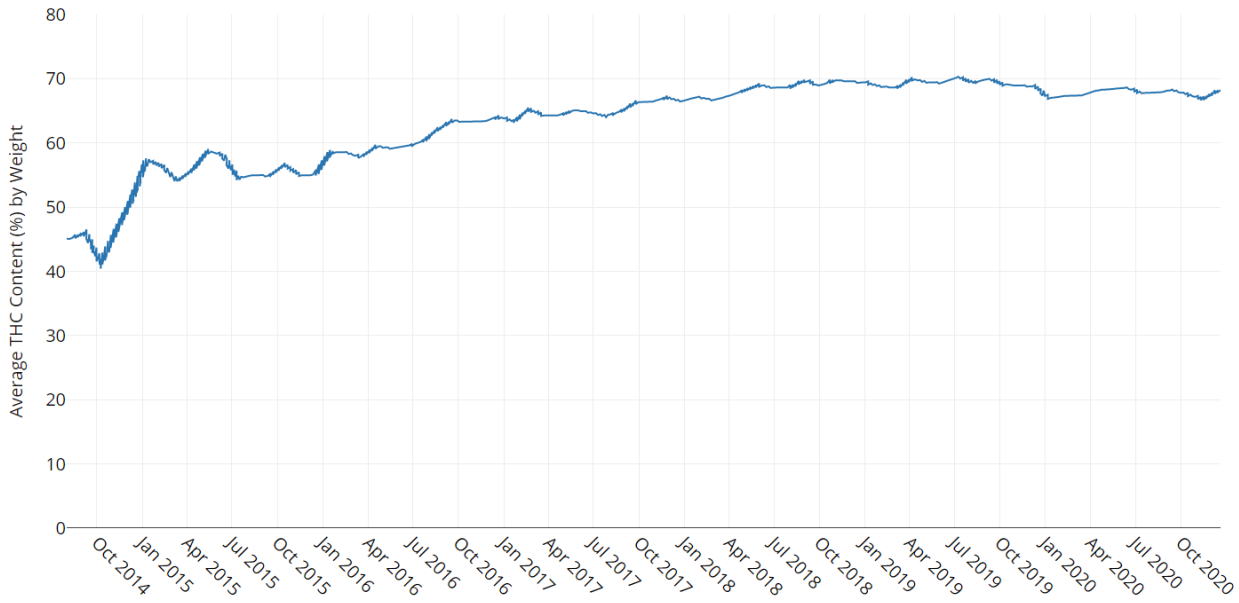


Figure 2: Average THC content (%) per gram of concentrates based on the data published by the Colorado Department of Revenue 2020 Marijuana Market Update Report.[2]



Funding was first received in the summer of 2021 from the State of Colorado, and, by the fall of 2021, the nucleus of the present review team (Appendix Table 2) had been constituted and the systematic review implemented in the form of a scoping review. This type of review has the purpose of identifying all available scientific studies so that more targeted reviews can be undertaken, if appropriate, based on the survey of what evidence is available. The critical output of this scoping review is an evidence map, which documents the topics covered by the literature.

Note: We offer the reminder that this is a focused review on questions related to the charge given to the ColoradoSPH by HB 1317. It is not a general review of the broad scope of issues related to public health and to beneficial/medical uses of cannabis and THC. Rather, the focus is "…on physical and mental health effects of **high-potency** THC marijuana and concentrates," per the charge to the ColoradoSPH. For those seeking information on marijuana and concentrates generally, there are general resources available, such as the CDC's Marijuana and Public Health page and NIDA's Cannabis (Marijuana) DrugFacts page. This report and the scope of our work under the charge of HB 1317 do not address cannabinoids other than THC.

At this point in filling the charge under HB 1317, the ColoradoSPH team has completed the scoping review including all studies informative on high-concentration products published by November 19, 2022. A Tableau dashboard has been implemented to access the evidence map so that the 452 studies meeting criteria can be filtered and utilized to address the charge given to the ColoradoSPH by the Colorado General Assembly. The team has now used the evidence map to address key, pre-specified questions related to policy matters that might be taken up by the legislature. These four questions (Table 1), referred to as Policy Questions in this report, were

identified based on our interpretation of the charge given to the ColoradoSPH and on input from the Scientific Review Council.

In prior discussions with the Scientific Review Council, there was agreement that there were two general approaches to utilizing the evidence map: (1) describing the scope of evidence available on major health outcomes ("bottom-up" approach); and (2) characterizing the evidence available to address the a priori Policy Questions ("top-down" approach). The former involves reviewing the studies within the major categories of health outcomes to identify clusters of studies addressing common questions that might support a further systematic review; and the latter refers to using the evidence map to identify the studies relevant to pre-specified Policy Questions. These two approaches were reviewed with the Scientific Review Council on November 21, 2022, who agreed with this bi-pronged approach.

This report includes studies that were directed at characterizing adverse consequences of high-concentration products and also studies directed at assessing possible beneficial uses. The charge to the ColoradoSPH directed us to look at "effects," without specification to restrict the review to effects construed as adverse or beneficial. Specifically, the charge did not direct us to consider only adverse, e.g., harmful effects. Consequently, we separately present the findings for these distinct "effects" as construed as either adverse or beneficial by the authors of the research reports considered in this review.

This report describes findings applying the top-down approach to the evidence map relevant to the four Policy Questions (Table 1). For each question, we have considered the studies available on the question and provide a narrative summary of the evidence identified. We provide a qualitative summary of the relevant evidence and conclusions on the availability of evidence relevant to each of the questions. The report offers recommendations. Finally, the report provides an update on the status of the development of the educational campaign.

Table 1. The Four Policy Questions

Question	**Policy Implication**
1. Are adolescents and young adults especially susceptible to adverse physical or mental health outcomes of high-concentration cannabis products?	What policies or regulations, if any, should be put in place to mitigate the adverse outcomes from high-concentration cannabis products on adolescents and young adults?
2. Are individuals with preexisting mental health conditions especially susceptible to adverse mental health outcomes of high-concentration cannabis products?	What policies or regulations, if any, should be put in place to mitigate the adverse outcomes from high-concentration cannabis products on those with preexisting mental health conditions?

3. Are pregnant and nursing women susceptible to adverse physical or mental health outcomes of high-concentration cannabis products? Are infants/children with prenatal and postnatal exposure to high-concentration cannabis products susceptible to adverse physical, neurodevelopmental or cognitive effects from this exposure?	Should warnings be placed on products? Should clinical providers systematically check for use of high-concentration products during and after pregnancy?
4. Are high-concentration THC cannabis products associated with greater risk of adverse physical or mental health outcomes than lower-concentration products?	Should restrictions be placed on high-concentration cannabis products and if so at what concentration level?

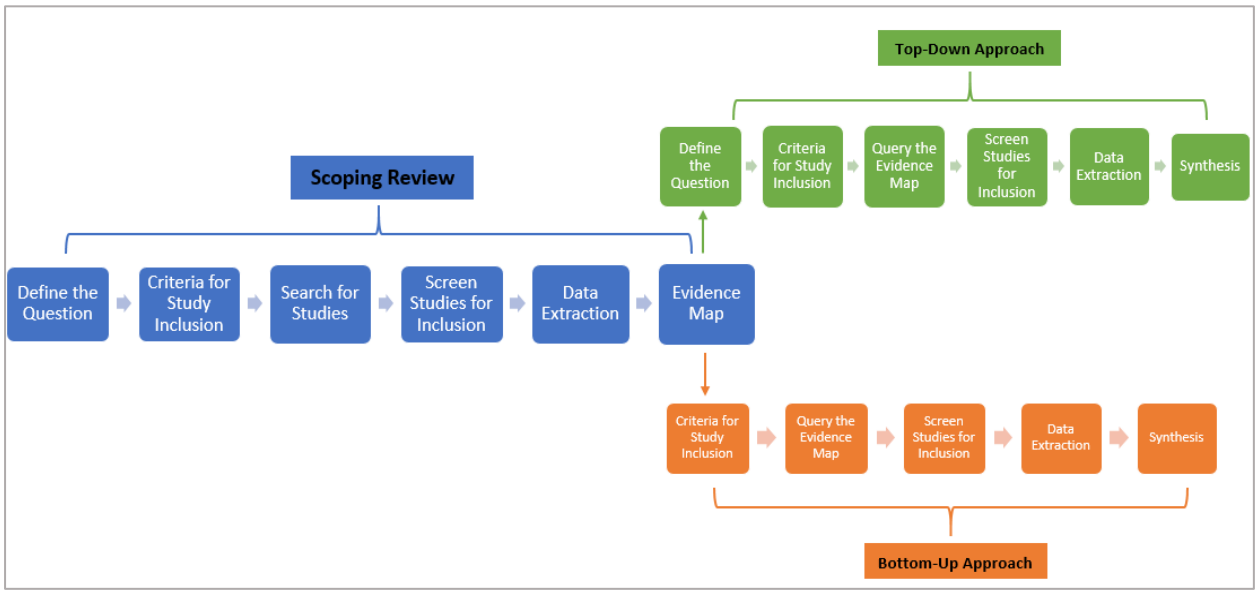
METHODS

Overview of the Approach for Developing the Evidence Map

The conduct of the scoping review followed a highly structured, rigorous, and reproducible approach established in the published protocol to minimize bias and errors. Briefly, the scoping review aimed to 'map' the range, extent, and nature of research relevant to understanding both the beneficial and adverse health outcomes of using high-concentration THC products. Our inclusion criteria were broad, and our search strategy was comprehensive. The screening of titles and abstracts was assisted with the artificial intelligence text-mining features available in Distiller®–the software we used for managing screening and data collection for this project. Two independent reviewers evaluated each full text record for its suitability for final inclusion. One reviewer extracted data from eligible records into an online form developed and managed in Distiller®; the data extracted were verified by another reviewer.

The output from the scoping review is an evidence map that characterizes all included studies. An interactive version of the evidence map that presents data at the study level is accessible through a Tableau dashboard. We will make the evidence map publicly available as a resource for public health purposes. The evidence map provides an overview of all research studies identified and can be used to: (1) describe the research on a particular topic, (2) to identify studies that can address a particular question (referred to as the 'top-down approach' in Figure 3), and (3) to identify clusters of similar studies that are suitable for subsequent systematic reviews (referred to as the 'bottom-up approach' in Figure 3).

Figure 3. Relationship between scoping review and top-down, bottom-up approaches.



Applying the Top-Down Approach

Description of Methods

We began by developing a priori Policy Questions to drive and guide the evidence-review process. In generating the four questions considered in this report (Table 1), we adhered to the intent of HB 1317 as the starting point, along with input from the Scientific Review Council. As a general approach to addressing the four questions, the review team queried the evidence map and screened the studies selected from the evidence map to determine the relevance of each record for answering the Policy Question of interest.

The seven-member research team (Tung, Wang, Brooks-Russell, Leslie, Oberste, Yim, Rittiphairoj) reviewing the studies and developing the evidence tables followed this general approach and harmonized and cross-validated their work to assure standardization. For the four Policy Questions, randomized control trials (RCTs) and observational/epidemiological studies were included, while case reports and case series were excluded. Additional inclusion criteria for each Policy Question are given below:

Policy Question 1: Studies with adolescent (9-17) or young adult (18-24) participants only, with no other age group included in the study.

Policy Question 2: Studies that included eligibility criteria for psychiatric health conditions, regardless of relevancy as described below.

Policy Question 3: Studies with participants who were pregnant (any trimester), postpartum, or breastfeeding; OR studies that included offspring who were in utero (any trimester) or preconception; OR studies with any pregnancy related outcome; OR studies with any pre-, peri-, and neonatal outcomes.

Policy Question 4: Studies that report a numeric THC value for products used and that were classified as high- or medium-relevancy as described below.

We reviewed all studies and further sorted them into three categories in terms of relevancy to the question at hand: high-, medium-, and low-relevancy. For a study to be considered high relevancy, it needed to address a direct association between high-concentration product exposure and the outcome.

Additionally, high-relevancy articles included data on each of the following exposure characteristics: (1) a numeric THC concentration above 5 mg THC or 10% THC, (2) the frequency of cannabis use, and (3) the duration of cannabis use. For a study to be considered medium-relevancy, it needed to include two of the three exposure characteristics needed for high-relevancy. All other studies were classified as low-relevancy. Studies including multiple exposure measures were assigned relevancy based on the most salient possible exposure (e.g., a study with full dose-response information for two products, one at 17 mg THC and one at 3 mg THC would be considered high-relevancy and our focus would be on the outcomes associated with the 17 mg THC product).

For Policy Questions 1, 2, and 3, the team reviewed the full texts of all studies, regardless of relevancy categorization. For Policy Question 4, due to the large number of studies identified after querying the evidence map (N= 290), the team did not review the full texts of low-relevancy studies (N = 187), leaving a total of 103 studies reviewed. The team then further assessed the studies to capture their characteristics and to determine the outcomes to which the results applied. Studies could contribute evidence for more than one Policy Question or for multiple outcomes within a Policy Question. Any study that was found to not be relevant during the full-text review was excluded at this stage. Information on excluded studies, including the reasons for exclusion, is provided in Appendix Tables 3, 4, and 5.

Characterization of the Evidence Available

To address the four Policy Questions, we provide a narrative summary of relevant studies identified for each question. Intentionally, the narrative summaries lack critical components of the full systematic review process, such as rating the risk of bias (or internal validity) of studies included in the summary. In addition, the summaries do not use structured consensus methods, such as Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) or the Navigation Guide to rate the certainty of the evidence. These methods were not considered appropriate for this broad assessment of a very heterogeneous and large body of literature. Therefore, for the narrative summaries conducted, we evaluate the evidence as recommended in the Synthesis without Meta-Analysis Guidelines.[3] Our goal is to provide a qualitative synthesis of a very heterogeneous body of evidence for each of the four questions. For each question, we evaluate the total number of studies available and the number of studies with statistically significant results, either favoring adverse or beneficial outcomes.

We also summarized the evidence using a "vote-counting" approach; that is, for each outcome relevant to a question, we count the number of studies with statistically significant associations for an adverse or beneficial effect and the number of studies with associations that are not statistically significant. The number of included studies that did not perform statistical tests is noted.

For Policy Questions 2 and 4, we classified these studies by whether statistical significance testing was carried out and if so then whether the findings showed (1) a significant association, (2) a non-statistically significant association, or (3) not assessed. A study was classified as showing an "effect" if it demonstrated at least one statistically significant association with the outcome of interest in the study's final analysis. A study was classified as having "no effect" if the study conducted a final statistical test or tests but none of the tests of association were statistically significant. Finally, a study was classified as "not assessed" if the report only provided descriptive statistics without testing statistical significance of associations. These classifications were applied to both measures of exposure dose (including frequency and duration of use) and concentration (mg THC or % THC).

Also, during full-text review, team members characterized the findings for the outcomes as 'beneficial' or 'adverse' for each study, using the study's definitions of adverse or beneficial. Thus, a study could provide results relevant to both beneficial and adverse effects, e.g., a study of possible beneficial effects during which adverse events occurred. This classification allowed comparison of the findings for both beneficial and adverse effects for a particular outcome. For a particular study, if results for one or more outcomes within an outcome domain were in a single direction of association (beneficial or adverse), then the team member reported that single direction of effect on the table. For Policy Questions 2 and 4 these classifications are reported in Appendix Tables 6 and 7 (see Table 2 below for illustration). In these tables, green boxes indicate statistically significant beneficial effects, red boxes indicate statistically significant adverse effects, grey boxes indicate no statistically significant beneficial or adverse effects, and a dash indicates that there was no statistical significance testing for a beneficial or adverse effect. In addition, Appendix Tables 6 and 7 include cannabis exposure information (product, THC concentration, purpose, route, frequency, and duration) from the evidence map for each included study.

Last, for each Policy Question and outcome domain, we develop a rating for the amount of the available evidence based on the number of statistically significant studies. The number of studies are classified as: none, limited (1-4), moderate (5-9), and substantial (10+). With this approach, we capture the quantitative scope of the evidence available and provide a qualitative summary of the findings in the narrative. Our approach should be distinguished from a more holistic integration of all relevant streams of evidence, potentially including pharmacological considerations, animal studies, and other types of research. Such broad integrations are carried out to judge the totality of the strength of evidence for a causal association.

Table 2: Sample of Appendix Tables 6 and 7.

Article	Direction of Association		Cannabis Exposure						
	Dose	Concentration	Product	THC Concentration		Purpose	Route	Frequency	Duration
				Low	High				
Neurologic Outcomes									
Ungerleider 1987[28]	■	■	Unspecified	2.5 mg	15 mg	Other	Ingestion	Daily	New user, Experienced user
Brunt 2014[14]	■	■	Cannabis	6%	19%	Medicinal	Inhalation, Ingestion	Daily	Other
Hunault 2014[15]	■	■	Cannabis	29.3 mg	69 mg	Other	Inhalation	Other	Other
Schloss 2021[2]	-	-	Oil	6.9 mg	27 mg	Medicinal	Sublingual	Daily	Chronic

*Average THC reported, THC correlated with outcome.
■ = Statistically significant beneficial effect
■ = Statistically significant adverse effect
■ = No statistically significant beneficial or adverse effect
- = No significance test for beneficial or adverse effects

RESULTS

Policy Question One: Are adolescents and young adults especially susceptible to adverse physical or mental health outcomes of high-concentration cannabis products?

Study Identification

Initial query of the evidence map identified 18 studies that focused on adolescents or young adults only. After reviewing each of the 18 publications, only two studies were determined to pertain to the Policy Question at hand.[4, 5] Appendix Table 3 provides information on the 16 excluded studies.

Narrative Study Description

Hines et al. performed a cohort study using data from the Avon Longitudinal Study of Parents and Children, a UK birth cohort of participants enrolled between 1991 through 1992 who were followed until 24 years of age.[5] The researchers found that those participants (N=141, 13%) who reported the use of high-concentration cannabis (defined as ≥ 10% THC; skunk/other stronger types of herbal cannabis) had an increased frequency of cannabis use, cannabis abuse, and anxiety disorders compared with those not using such products. When adjusted for frequency of use, use of high-concentration cannabis was no longer statistically associated with psychotic experiences, tobacco dependence, and other illicit drug use.

Leventhal et al. used data from the Happiness and Health survey study, a cohort study of children in 10 high schools in the Los Angeles area.[4] Past 30-day use prevalence figures in the overall sample of 3,177 adolescents were 13.5%, 7.9%, and 4.9% for combustible, edible, and vaporized

cannabis products, respectively. The investigators compared drug use and psychiatric outcomes amongst students who did and did not use cannabis, in addition to comparing cannabis users based on preferred form of use. The authors reported that all forms of non-cannabis substance use, and all psychiatric symptoms and traits were positively associated with combustible, edible, and vaporized cannabis product use. The magnitude of comorbidity did not significantly differ by cannabis product type. However, psychiatric comorbidities were more frequent in poly-product cannabis users.

In summary, Hines et al. did conclude that "high-potency" cannabis was associated with mental health conditions and substance use. However, when the frequency of use was included in the analysis, those associations were attenuated. This attenuation means that concentration alone was not responsible for the observed effects; frequency also contributed. Leventhal et al. did not find differences in psychiatric symptoms/traits and other drug use by cannabis product type (combustible, edible or vaporized).

Findings

Only two studies relevant to Policy Question One were identified.[4, 5] Associations were found for some symptoms with measures of cannabis product used. However, the evidence is limited in quantity, and further research is needed on this Policy Question. The studies are classified as providing a **Limited Amount of Evidence.**

Policy Question Two: Are individuals with preexisting mental health conditions more susceptible to adverse mental health outcomes of high-concentration cannabis products?

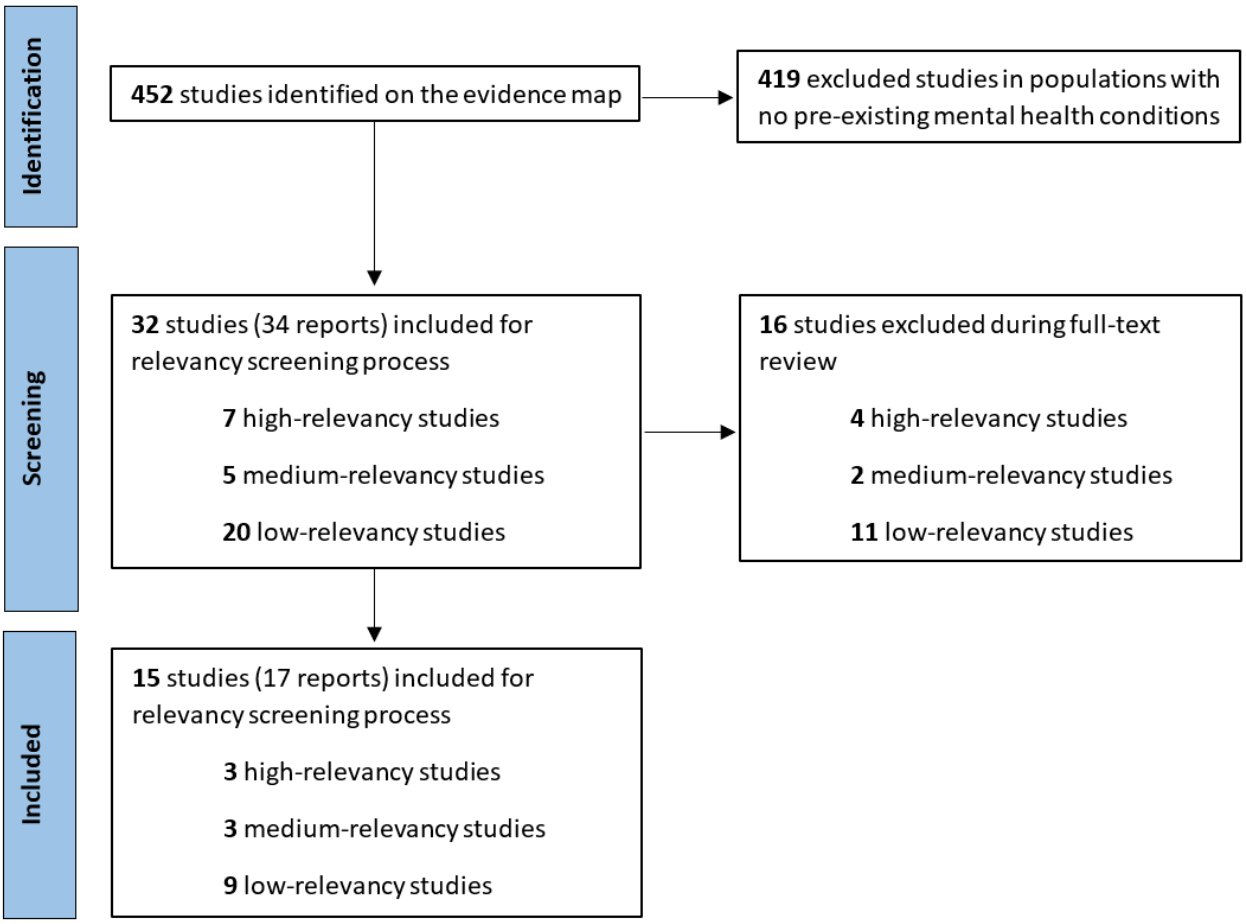
Study Identification

Initial query of the evidence map identified 32 studies (four RCTs and 28 observational studies) that included individuals with preexisting mental health conditions. While the question at hand is focused on adverse outcomes, we also included studies that examined beneficial applications of THC-containing products. After full manuscript review, 15 studies were found to be relevant to addressing the question (Figure 4). Two found associations with THC concentration and adverse outcomes, while six found associations with beneficial outcomes.

A range of mental health conditions was covered in the 15 studies, and the types of effects and extent of evidence were specific to each mental health condition. Below, we describe the evidence specific to adverse outcomes for each mental health condition and collectively for beneficial outcomes. Information on the included studies is provided in Appendix Table 6 and information on the excluded studies is provided in Appendix Table 4. Appendix Table 6 details: (1) all study reports determined to be relevant after full-text review; and (2) coding of findings

from each study as adverse, beneficial, showing no effect, or not assessed. We code the findings on each outcome in each study to both dose and THC concentration.

Figure 4: Study Flow Diagram for Addressing Policy Question 2.



Adverse Outcomes: Mental Health Conditions

Four studies with six reports examined this outcome.[6-11] The findings of each study are counted only once to avoid double-counting, given the multiple published reports from the singular study. For studies with multiple published reports, we have referenced the primary report to avoid double-counting.

In the first study, Genetics and Psychosis (GAP) case-control study[7, 8, 12], a report by Di Forti et al. found that any cannabis use, daily use, cannabis initiation prior to 15 years of age, and "high potency" use (HR=1.48, 95% CI: 1.17 - 2.04) were all associated with earlier age of first onset of psychosis.[8] The GAP study also found an association between high-concentration cannabis use (vs no use) and first episode psychosis (OR=2.92, 95% CI: 1.52-3.45) as well as everyday use and first episode psychosis (OR=3.04, 95% CI: 1.91-7.76).[7] This study also examined the

potential interaction between child abuse and high-concentration cannabis and the association with psychotic disorders. The study found that the use of high-concentration cannabis was associated with psychotic disorders (OR=2.16, 95% CI: 1.15 - 4.06).[12]

The second study was part of the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) and examined the relationship between cannabis use and psychotic symptoms. The study found an association between premorbid cannabis use and symptoms of psychosis.[10] The EU-GEI study also found that daily cannabis use was associated with increased odds of psychotic disorder compared with never users (aOR=3.2, 95% CI: 2.2-4.1), and there was much higher odds for daily use of "high-potency" types of cannabis (aOR=4.8, 95% CI: 2.5–6.3).

The third study examined chronic/relapse of psychosis. Schoeler et al. did not find a statistically significant association between relapse of psychosis and high-concentration cannabis (OR=2.63 95% CI: 0.91 7.91).[13]

The fourth study examined the severity of symptoms associated with cannabis use one week prior to admission among psychiatric inpatients. Madero et al. found an association between cannabis use operationalized as standard joint units (SJU) in a bivariate analysis but in the full multivariate analysis, SJU was not statistically associated with symptom severity as measured by the Brief Psychiatric Rating Scale (BPRS).[14]

We conclude that there is a **Limited Amount of Evidence** (two statistically significant studies of 15 total studies) that high-concentration THC cannabis products are associated with adverse mental health outcomes for those with preexisting mental health conditions.

Beneficial Outcomes: Mental Health Conditions

We identified 11 studies that examined beneficial outcomes related to the use of high-concentration cannabis in individuals with a pre-existing mental health condition. Shelef et al. examined the behavioral and psychological symptoms of dementia in Alzheimer's patients and found significant decreases in delusions, agitation/aggression, irritability, apathy, and sleep associated with administration of medical cannabis oil.[15]

One study examined chronic/relapse of psychosis. Matsumoto et al. found that measures of THC dose and concentration were associated with reduced risk of chronic psychosis (OR=0.114, 95% CI: 0.023 – 0.556).[16]

Two studies examined the symptoms of obsessive-compulsive disorder (OCD). Kayser et al. used a randomized, placebo-controlled, within-subjects design and concluded there was no impact on OCD symptoms of cannabis treatment.[17] Mauzay et al. reported descriptive statistics from an app used by medical cannabis patients.[18] This study found a 60% reduction in compulsions, a 49% reduction in intrusions, and a 52% reduction in anxiety immediately after cannabis use, but no change in baseline symptom severity.

Casarett et al. examined the use of cannabis for palliative care symptoms through patient self-report and found that patients reported improved neuropathic pain, insomnia, and depressive symptoms with cannabis use.[19]

A study conducted by Hergenrather et al. examined the use of medical cannabis to treat attention deficit hyperactivity disorder (ADHD).[20] This self-report questionnaire study found an association between higher-dose consumption of medical cannabis and ADHD medication reduction and also that higher doses of CBD was associated with lower Adult ADHD Self-Report Scale (ASRS) score.

Two studies explored the use of cannabis for treatment of PTSD symptoms and patients. LaFrance et al. reported that higher doses of cannabis were associated with larger reductions in self-reported intrusions and anxiety.[21] Baseline severity of symptoms remained constant over time. Bonn-Miller et al. found no significant difference between placebo and treatment groups in reducing symptoms of PTSD.[22]

A study conducted by Stith et al. looked at the use of cannabis to reduce symptoms of anxiety, stress, and agitation.[23] The study found that any use of cannabis was associated with a reduction in symptoms, and that products containing mid- to high-levels of THC were statistically significant predictors of symptom relief.

The remaining two of the 11 studies examined use of medical cannabis for the treatment of depression symptoms. Li et al. used self-report data and generally concluded that the vast majority of patients experienced anti-depressive effects and that the highest THC concentration category (20-35%) was associated with the greatest symptom relief.[24] Cuttler et al. similarly used self-report and found that patients experienced the greatest relief from depressive symptoms using high-CBD/low-THC strains, while gaining the most relief from stress with high-CBD/high-THC strains.[25]

We conclude that there is a **Moderate Amount of Evidence** (six statistically significant studies of 15 total studies) that high-concentration THC cannabis products are associated with beneficial outcomes for those with preexisting mental health conditions.

Findings

A total of 15 studies relevant to Policy Question Two were identified. Of these, four identified associations between cannabis use and adverse outcomes with two of those four demonstrating a statistically significant association between THC concentration and increased risk for first episode psychosis. One study examined the association between chronic/relapse psychosis, and found a negative association. A fourth study found an association with dose but not with THC concentration for the severity of symptoms.

The remaining 11 studies explored associations between cannabis use and beneficial outcomes for a variety of conditions including Psychosis, PTSD, Depression, Anxiety, ADHD, and OCD. For these 11 studies relating to beneficial outcomes, the evidence is limited for the individual

conditions, e.g., PTSD and ADHD. The significant findings for benefits for some outcomes indicate that more research may be justified, but the literature is too limited in scope to serve as a rationale supporting therapeutic interventions.

We propose that a systematic review, including risk of bias assessment for each included study, should be conducted for the studies addressing the adverse outcomes for psychosis.

Policy Question Three: Are pregnant and nursing women susceptible to adverse physical or mental health outcomes of high-concentration cannabis products? Are infants/children with prenatal and postnatal exposure to high-concentration cannabis products susceptible to adverse physical, neurodevelopmental or cognitive effects from this exposure?

Study Identification

Initial query of the evidence map identified six studies that included pregnant or nursing women; their offspring in utero or preconception; any pregnancy related outcomes; or any pre-, peri-, or neonatal outcomes. None of the studies examined a direct association with cannabis use and health outcomes in pregnant and nursing women or infants/children with prenatal or postnatal exposure. Thus, this probing of the evidence map identified no studies contributing findings relevant to Policy Question Three. Information on the excluded studies is provided in Appendix Table 5.

Findings

No studies were identified for this Policy Question; that is, the evidence is classified as **None**.

Policy Question Four: Are high-concentration THC cannabis products associated with greater risk of adverse physical or mental health outcomes than lower-concentration products?

Overview

Evidence relevant to this question is particularly germane to regulatory or other measures that might be taken by the Colorado General Assembly or other entities. By its nature, the number of studies relevant to Policy Question Four within the evidence map is substantial, greatly exceeding that for the other three Policy Questions. The evidence relevant to the question encompasses multiple outcomes across all population groups of interest. To handle this larger scope, we modified the approach taken for the other three questions. We describe the methods for Policy Question Four in the methods section below, supplementing the general description of our approach above.

Methods for Policy Question Four

The team adapted the approach described above, modifying the process outlined in the overall methods to handle the much larger volume of records for this question in a short timeframe by considering high- and medium-relevancy studies only. Consequently, low-relevancy studies were excluded from full-text review during screening (Figure 5). Because Policy Question Four addresses the possibility of a threshold, studies were excluded that did not compare two different THC concentrations, or that compared products only at a single THC concentration to a placebo. The remaining high- and medium-relevancy studies were then grouped based on coded outcome domains, with one study placed in multiple groups if multiple outcome domains had been coded (Table 3).

Figure 5: Study Flow Diagram for Addressing Policy Question 4.

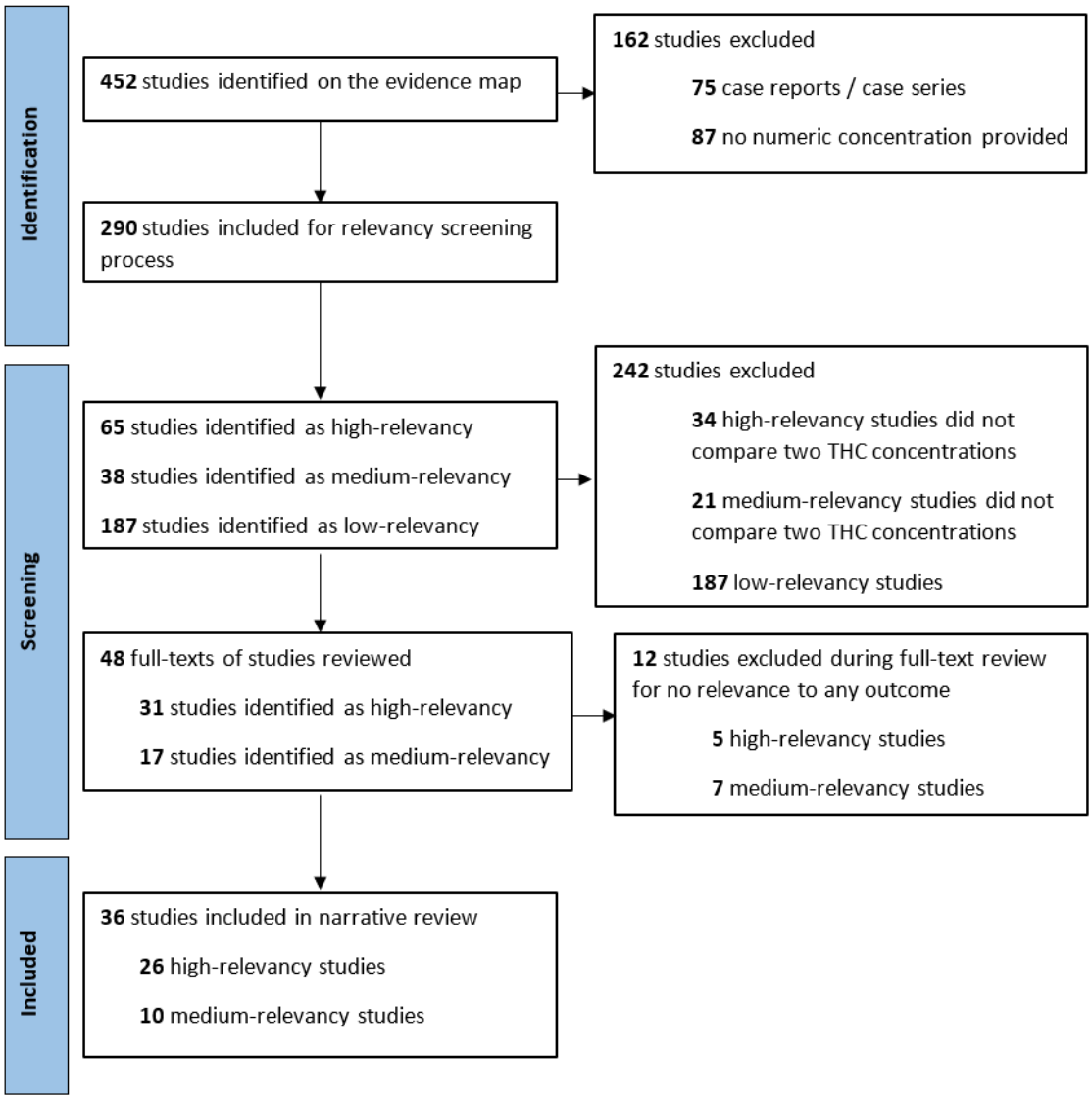


Table 3: Policy Question 4 Studies by Outcome Domain

Outcome Domains	High-relevancy studies, N= 26*	Medium relevancy studies, N = 10*
Cancer symptom management	2	0
Cardiometabolic	2	1
Gastrointestinal	1	0
Immunity	1	0
Driving Performance	5	1
Mental Health	14	5
Neurologic	3	1
Ocular	1	0
Pain	4	3
Pre-, peri-, and neonatal	0	0
Pregnancy	0	0
Psychosocial	9	0
Respiratory	2	0
Sexual and reproductive	1	0
Sleep	8	0
Substance use/dependence	4	0
Other	6	1

*Most studies report multiple outcomes, so each column will not add to the total number of studies

Literature Selected

Forty-eight studies were identified as meeting the criteria for high- (N=31) or medium- (N=17) relevancy (Figure 5). Of these, ten were determined to be not relevant after a full text review, resulting in 36 total studies (high: N=26; medium: N=10) included in the narrative synthesis. Table 3 provides the distribution of the outcome domains covered by the 36 studies. The most populated domain was mental health followed by the sleep and pain domains.

Narrative Descriptions by Outcome

Below, we provide narrative descriptions of the studies by outcome. In each outcome section, we begin by detailing the number of studies included in our initial query of the evidence and the number of studies determined to be relevant after a full-text review. We conclude each section by providing a narrative description that summarizes the scientific literature specific to each outcome. Appendix Table 7 provides details by outcome: (1) all studies determined to be relevant after full-text review; and (2) coding of each outcome from each study as adverse, beneficial, no effect, or not assessed. We code the findings on each outcome in each study to both dose and THC concentration.

Adverse Outcomes

Cancer Symptom Management

We identified two studies addressing associations between the use of high-concentration THC products and symptom management in cancer patients. After full manuscript review, both studies were determined to be relevant to addressing the question.

One study showed a statistically significant association between high-concentration THC cannabis and a relative decrease of quality of life compared with low-concentration THC while the second showed no association.[26, 27]

We conclude that there is a **Limited Amount of Evidence** (one statistically significant study of two studies total) that high-concentration THC cannabis products are associated with more adverse outcomes when used for cancer symptom management.

Driving Performance

Query of the evidence map identified nine studies addressing associations between the use of high-concentration THC products and risk of injury from a motor vehicle accident or with driving performance assessed with a simulator. After full manuscript review, six studies were determined to be relevant to addressing the question.

In an observational study, López-Pelayo et al. found that cannabis use before 18 years of age and use duration of at least 7.5 years, but not immediate factors such as product concentration, were associated with increased risk of being in a motor vehicle crash.[28] Five studies examined simulated driving performance. Marcotte et al. found decreased simulator driving ability with cannabis use but no difference in performance with use of low-concentration (5.9% THC) versus high-concentration (13.4%) THC products.[29] Lenne et al. compared two concentrations of THC (one 19 mg THC cigarette or two 19 mg THC cigarettes) and found that there was a concentration-dependent negative change in driving performance.[30] In this study, more experienced users of cannabis had less of a concentration-dependent response for reduced performance than less-experienced users. Ronen et al. compared two concentrations of THC and placebo and found a statistically significant relationship between THC concentration and driving measures.[31] Hartley et al. also compared two concentrations of THC and placebo but found no clear association between THC concentration and driving performance measures.[32] Finally, Rafaelsen et al. compared three concentrations of THC and placebo and found a statistically significant association between THC concentration and driving measures.[33]

We conclude that there is a **Limited Amount of Evidence** (three statistically significant studies of six studies total) that high-concentration THC cannabis products are associated with adverse driving performance outcomes.

Mental Health

Query of the evidence map resulted in 19 studies that met the criteria for high-relevancy and five for medium-relevancy. After full text review, all of these studies were determined to be relevant to addressing the question.

Four studies reported mental health outcomes but did not assess the statistical significance of associations.[34-37] Of those that did tests of significance, two studies did not find statistically significant associations of mental health outcomes with concentration or dose. Two other studies found no significant associations with concentration alone. The remaining studies, all of which demonstrated a statistically significant association with concentration, included eight showing adverse health effects and four with beneficial effects. The studies that examined adverse health effects are described below.

Steeger et al. surveyed 300 adult recreational users of cannabis concentrates, edibles, and flower products.[38] For all products combined and for concentrates, they found a significant association between past month frequency of use and symptoms of depression and anxiety, which was not the case for flower and edible frequency of use alone. After controlling for average frequency of use across all product forms and CBD concentration, they did not find an association between THC concentration of cannabis flower, edible, or concentrate and symptoms of anxiety and depression. The authors note there are potential issues with bias from self-reporting.

Drennan et al. enrolled 81 participants, randomizing them to THC-dominant (84.99% THC) or CBD-dominant (4.5% THC inhaled concentrate products).[39] Acute effects were assessed pre-use, immediate post-use, and one-hour post-use. The study reported that the THC-dominant concentrate was associated with increased paranoia immediately post-administration.

Brunt et al. recruited 102 participants on the satisfaction and subjective effects of three strains of medicinal cannabis THC high (19% THC), THC medium(12% THC), and THC low (6% THC).[40] The high and medium THC groups included both ingested (tea) or inhaled, the low THC group was inhalation only. The study found a difference between THC high and THC low, with the level of dejection being higher for the THC high group. The level of anxiety was also different among the cannabis groups with multiple comparisons indicating higher anxiety levels in the THC high group than in the THC low group.

Schlienz et al. conducted an RCT that involved administration of oral THC brownie edibles that contained 0, 10, 25, and 50 mg THC to 17 healthy adults.[41] Peak effects were noted at a hour and a half to three hours post-ingestion. The study indicated a dose-dependent association of increasing questionnaire subscales relating to adverse mental health effects. In the 50 mg THC group, there were statistically significant associations with paranoia, restlessness, and anxiousness/nervousness.

Sainz-Cort et al. investigated the differential effects of vaporized extracts on psychotic-like states (delusional thinking, perceptual distortion, mania) in 18 healthy adult current cannabis users (>3/week use).[42] The cross-over trial included four exposure groups (1) THC extract (65 mg), (2) CBD extract (130 mg), (3) THC (65 mg) + CBD (130 mg) extract, and (4) placebo (0.05 mg

THC, CBD). The THC only scores were higher than the THC + CBD scores for all subscales on the Psychotomimetic States Inventory (PSI). Addiction Research Center Inventory (ARCI) subscales (activation, sedation, and euphoria) were also higher with the high THC group. Subjective effects subscales (hearing voices and suspicious ideas or beliefs) were also highest with the high THC group. The high THC group outcomes were the most elevated at all timepoints up to 75 minutes.

Mueller et al. enrolled 86 participants in a randomized trial testing the difference between two age groups (21-25 and 55-70 years old) response to inhaled cannabis flower, separated into three concentration groups (24% THC:<1% CBD; 23% CBD:<1% THC; THC 9%:CBD 10%).[43] Averaging across age and study time, subjective anxiety was higher in the high THC groups. Older adults had higher anxiety in the high CBD group compared to the CBD + THC group one-hour after use.

Hines et al. surveyed 1087 people who used cannabis in the past year.[5] The authors tested the association of THC concentration with mental health and substance use outcomes. The exposure was self-reported as high-concentration (≥ 10% THC) or low-concentration (<10% THC). The study found little evidence that high-concentration product use was associated with moderate or severe depression. There was evidence that use of high-concentration cannabis was associated with an elevation in likelihood of generalized anxiety disorder and psychotic-like experiences. For psychotic-like experiences, after adjusting for frequency of use, the strength of association weakened.

Wildes et al. surveyed 150 adults who had been prescribed an opioid medication for persistent pain.[44] Investigators inquired about the frequency and average THC and CBD concentration (the product and route was omitted) along with health outcomes. The THC range was not reported, though 31 participants used products with an average THC concentration of 10% or greater. The mental health outcomes of depression and anxiety worsened as the past 30-day frequency, % THC concentration, and % CBD concentration increased.

Hunault et al. conducted a crossover RCT of 24 recreational users smoking cannabis cigarettes with four doses of THC (placebo, 29, 49 and 69 mg of THC) on four separate test days.[45] Anxiety measures reached a maximum within the first two hours after post-exposure with effects lasting up to eight hours. The 69 mg THC group had the highest anxiety scores at all timepoints.

Lopez-Pelayo et al. surveyed 2,124 participants with the exposure classified using SJU to create four groups by last month mg THC per day (0, 1-6, 7-14, 15-21 mg) and the validated surveys for health outcomes.[28] The authors note there was no association between mg THC per day over the last month and suicidal impulses, anxiety, or depression.

Schloss et al. conducted a RCT involving 88 adult patients diagnosed with a high-grade glioma receiving two different ratios of oral medicinal cannabis: oil-based organic whole plant extracts of cannabis based on a 1:1 and 4:1 ratio of THC:CBD (1:1 THC 4.6 mg/ml:CBD 4.8mg/ml and 4:1 THC 15mg/ml:CBD 3.8 mg/ml).[26] The 4:1 ratio group had more hallucinations at night that resolved following dose reduction but statistical tests for adverse events were not performed. The

quality-of-life subscales related to mental health generally favored the 1:1 group but were not statistically significant.

Peters et al. included 41 participants, randomized to five different concentrations (placebo, 5, 10, 15, and 20mg THC).[36] The 20 mg THC group had the highest proportion of psychiatric adverse events (paranoia, euphoric mood, restlessness) but no formal statistical significance testing was conducted.

Noyes et al. carried out an RCT testing the analgesic effects of oral THC on 10 cancer patients at four different concentrations (5, 10, 15, and 20 mg THC).[34] The highest proportions of mental health adverse events (disconnected thought, numbness, euphoria, visual hallucinations) were reported in the 20 mg THC group but no formal statistical test was conducted.

Prince et al. surveyed 156 participants about cannabis use within the past 30 days to examine associations with mental and physical outcomes.[37] Self-reported exposure were divided into vaporized flower and concentrate. The authors note a trend that participants reporting any or higher counts of mental health problems also reported "lower potency" products (Pearson's r=0.13, 95% CI: 0.30 to 0.04) except for more participants with depression symptoms also reporting "higher potency" products (Pearson's r 0.14, 95% CI: -0.03 to 0.31). For any mental health effects, there was a small effect association between higher counts with "higher potency" cannabis concentrate use, which was not found for use of flower products. The study analyses was based on the magnitude of effect rather than statistical significance testing.

We conclude that there is a **Moderate Amount of Evidence** (eight statistically significant studies out of 19 studies total**)** that high-concentration THC cannabis products are associated with adverse mental health outcomes.

Neurologic

Query of the evidence map found eight studies that met the criteria of high-relevancy, and four for medium-relevancy in the category of Neurologic Outcomes. After full manuscript review, four studies were determined to be relevant.

Hunault et al. compared recreational users who smoked cannabis cigarettes with four doses of THC (placebo, 29, 49 and 69 mg of THC) in a randomized, double blind, placebo-controlled, crossover study.[45] Dizziness was doubled with the highest (69 mg) dose compared to middle and low doses up to two hours post-smoking. Impairments in memory and concentration were seen with higher doses of THC, in addition to feeling less alert, calm and content. Sedation increased with higher doses of THC and increased by a factor of 5.7 with the highest THC dose (69 mg) compared to placebo.

Schloss et al. performed an RCT involving adult patients diagnosed with a high-grade glioma who received two different ratios of oral medicinal plant extracts of cannabis 1:1 THC 4.6mg/ml:CBD 4.8mg/ml and 4:1 THC 15mg/ml:CBD 3.8mg/ml.[26] Three (3.4%) participants had their dose reduced due to side effects which included shaking and hallucinations at night. An

additional 21% reported sleepiness/sedation and 6% reported mild hallucinations, paranoia or euphoria at night. However, the frequencies of these events were not analyzed for statistical significance.

We conclude that there is a **Limited Amount of Evidence** (one statistically significant study out of four studies total**)** that high-concentration THC cannabis products are associated with adverse neurologic outcomes.

Psychosocial

Query of the evidence map identified nine high- and three medium-relevancy studies addressing associations between the use of high-concentration THC products and psychosocial outcomes. After full-text review, three of the 12 studies were determined to be relevant to addressing the association of high-concentration cannabis with psychosocial outcomes.

Taylor et al. examined the acute effects of THC concentration on aggression (measured in a lab setting) and found that THC was not significantly associated.[46] Weinstein et al. found that decision making in a gambling task was acutely impacted after smoking 17 mg THC but not 13 mg.[47] Lopez-Pelayo et al. surveyed adults living in Spain on use in the last 30 days.[28] Frequency and mg of THC used in the past month were not significantly associated with measures of violence or cognitive impairment. Mostly absent from the studies included in this review are studies of the impact of high-concentration cannabis products on psychosocial outcomes such as individual functioning (beyond mental health) and relationships with family and friends. These are behaviors and characteristics that emerge over time and are challenging to study in relation to differing THC concentrations and dose.

We conclude that there is a **Limited Amount of Evidence** (one statistically significant study out of three studies total**)** that high-concentration THC cannabis products are associated with adverse psychosocial outcomes.

Sleep

Query of the evidence map identified 10 high- and two medium-relevancy studies addressing associations between the use of high-concentration THC products and sleep outcomes. After full review, eight studies were determined to be relevant to addressing the question of association of high-concentration THC cannabis products with sleep outcomes. Two studies did not include statistical significance testing for associations with THC concentration or dose.[36, 48] Two studies included significance testing but found no association between sleep outcomes and THC concentration or dose.[28, 49] One study found an association with the dose of THC but not with THC concentration.[50] One study found an association between high-concentration cannabis and adverse sleep outcomes.[51]

This study by Nicholson et al. investigated cannabis use in a healthy population.[51] It was a small study (eight participants) that examined combinations of THC and CBD on sleep and their

findings are consistent with THC having sedative effects. However, the study ultimately found adverse effects on sleep from high-concentration THC.

We conclude that there is a **Limited Amount of Evidence** (one statistically significant study of eight studies total**)** that high-concentration THC cannabis products are associated with adverse sleep outcomes.

Substance Use / Substance Dependence

Initial query of the evidence map resulted in nine studies addressing associations between the use of high-concentration THC products and substance use/abuse/dependence. After full manuscript review, four studies were determined to be relevant to addressing the question.

Three of the four studies did not find an association between high-concentration cannabis and measures of substance use/abuse/dependence.[28, 38, 52] Only the study by Hines et al. found that use of high-concentration cannabis was associated with self-report of cannabis abuse.[5] All four of these studies, however, found associations between increased dose and more specifically frequency of cannabis use and measures of substance use/abuse/dependence.

We conclude that there is a **Limited Amount of Evidence** (one statistically significant study of four studies total**)** that high-concentration THC cannabis products are associated with adverse substance use/dependence outcomes.

Other Health Outcome - Dry Mouth

Four papers were found in the evidence map that met the criteria and contained an outcome related to dry mouth. All four papers reported dry mouth as an adverse event but not as a primary outcome. Peters et al. is a pharmacokinetic study that tested five different doses of THC and included adverse events sorted by various health outcomes. The study did not conduct formal statistical tests for these adverse events.[36] Hunault et al. is a study on subjective effects of three different doses of THC and a placebo and suggests that there is a relationship between THC concentration and dry mouth.[45] Both Cousens et al. and Gustavsen et al. reported dry mouth as an adverse event with cannabis use but do not include a statistical analysis of this outcome.[53, 54]

We conclude that there is a **Limited Amount of Evidence** (one statistically significant study of four studies total**)** that high-concentration THC cannabis products are associated with dry mouth.

Beneficial Outcomes

Mental Health

Query of the evidence map resulted in 19 studies that met the criteria for high-relevancy and five for medium-relevancy. After full text review, 19 of these studies were determined to be relevant.

Three studies reported mental health outcomes but did not assess statistical significance. Of those that did, there were no statistically significant associations with mental health effects and concentration or dose for two studies. A further two studies found no association with concentration alone. The remaining studies included eight showing adverse health effects and five with beneficial effects. The five studies that examined beneficial effects are summarized below.

Li et al. used self-report via an electronic application to survey 819 participants who used combustible medical cannabis for symptoms of depression.[55] THC groups included (1) THC <10%, (2) THC 10-19%, and (3) THC 20-35% concentration. Their results suggest that, when labeled plant phenotype and combustion method are controlled for, THC was the strongest independent predictor of symptom relief.

One study found a signficant association with dose but not with concentration.[56] Mauzay et al. used electronic data collection to assess control of symptoms in 87 individuals self-identifying as having OCD.[18] They did not find evidence of a difference in mixed models testing association of the THC concentration of inhaled cannabis with intrusions, compulsions, or anxiety symptoms. There was a significant association with increased dose (# of puffs) and decreased compulsions.

Casarett et al. also used self-report via electronic data collection to survey a total of 2,431 participants for changes in symptoms of neuropathic pain, anorexia, anxiety, depression, insomnia, and PTSD-related flashbacks with vaporized cannabis.[19] They reported % THC as a ratio of THC:CBD (divide the THC content by the sum of THC and CBD content). There was a statistical association between increased THC:CBD ratio and improved depressive symptoms. The study also found that higher THC:CBD ratios were not associated with a greater response for post-traumatic stress disorder (PTSD)-related flashbacks, anxiety, or anorexia.

Stith et al. similarly used electronic data collection to survey 3,341 participants about cannabis use across multiple product types though the report focusing on inhaled (vape, pipe, joint) cannabis flower.[57] They reported that participants treating depression had greater symptom improvement from inhaled flower in the 10-19% and 19-34% THC groups relative to the 0-9% THC group. There was no statistically significant association in symptom relief for anxiety in these groups.

Drennan et al. reported beneficial effects as well as the adverse effects listed in the harms section.[39] The study reported a statistically significant increase in elation with any THC use. After one hour, THC-dominant concentrate had a larger effect lowering anxiety.

Wan et al. surveyed 837 participants on their use of medical cannabis over a four-month period.[35] Various cannabis strains were reported alongside symptoms but no statistical comparisons were made.

We conclude that there is a **Limited Amount of Evidence** (four statistically significant studies of 19 studies total**)** that high-concentration THC cannabis products are associated with beneficial mental health outcomes.

Neurologic

Query of the evidence map found eight studies that met the criteria of high-relevancy, and four for medium-relevancy in the category of Neurologic Outcomes. After full manuscript review, four studies were determined to be relevant.

Brunt et al. evaluated satisfaction and subjective effects of using medicinal cannabis in people who used one of three groups of cannabis strains: 19% THC/less than 1% CBD (n = 48), 12% THC/less than 1% CBD (n = 29), and 6% THC/7.5% CBD (n = 25).[40] There was no evidence of differences in subjective neurologic symptoms reported including alertness, tranquility, fatigue, irritability, disorientation, dizziness amongst the three strains.

Ungerleider et al. performed a double-blind, placebo-controlled, crossover trial of escalating doses of oral THC (2.5-15 mg) in 13 participants with clinical multiple sclerosis and spasticity.[58] At higher THC concentrations, there was significant improvement in spasticity. A threshold of improvement was noted at concentrations greater than 7.5 mg in patient ratings of spasticity compared with placebo. There were no significant adverse events at higher concentrations compared with lower concentrations.

We conclude that there is a **Limited Amount of Evidence** (one statistically significant study of four studies total**)** that high-concentration THC cannabis products are associated with beneficial neurologic outcomes.

Pain

Query of the evidence map identified 12 studies addressing direct associations between THC concentration and pain outcomes. After full manuscript review, seven studies were determined to be relevant to addressing pain as an outcome.

Casarett et al. used a retrospective cohort study design and reported that an increased THC:CBD ratio was associated with neuropathic pain response (OR = 3.58; 95% CI: 1.32–9.68).[19]

Noyes et al. reported a significant difference of pain relief scores between low-concentration THC (5 and 10 mg) and high-concentration THC (15 and 20 mg), suggesting that higher concentrations of THC are related to greater pain relief.[34]

Schloss et al. 2021 used a single-center Phase II double-blind randomized design. In this study 1:1 THC 4.6 mg/ml:CBD 4.8 mg/ml was used as low THC concentration and 4:1 THC 15 mg/ml:CBD 3.8 mg/ml was used as high THC concentration.[26] This study found that the higher THC concentration decreased pain levels at each time point but the differences were not statistically significant.

Four additional studies found no association between different THC concentrations and pain outcomes. Prince et al. compared flower (20% THC) and concentrated cannabis products (76% THC).[52] In this study, they reported there was not a significant association between pain and THC concentration. Stith et al. used the mobile device software, ReleafApp to record self-report

survey.[57] The study found that differences in THC concentration was not associated with symptom relief for back pain. A second Stith et al. study found that different concentrations of THC for the treatment of headache and migraine were not significant.[59] Gustavsen et al. carried out a prospective observational study and reported no difference in relief of neuropathic pain between high-concentration THC DROPS (25 mg THC, <2 mg CBD/mL), 1:1 DROPS (12.5 mgTHC and CBD/mL) and low-concentration CBD DROPS (25 mg CBD, 2 mg THC/mL).[48]

We conclude that there is a **Limited Amount of Evidence** (two statistically significant studies out of seven studies total**)** that high-concentration THC cannabis products are associated with beneficial pain outcomes.

Other Health Outcome - Perceived Health

Three studies were found in the evidence map that met criteria and contained an outcome related to perceived health and all three were determined to be relevant. The three studies used cross-sectional data to evaluate relationships between various symptoms and high-concentration THC cannabis products.[37, 38, 57] Steegler et al. and Stith et al. found statistically significant association between high-concentration THC cannabis products and greater perceived health, but it is important to note that in both cases general health was measured by participant perception. Prince et al. did not find a statistically significant association between high-concentration cannabis products and perceived health.

We conclude that there is a **Limited Amount of Evidence** (two statistically significant studies out of three studies total**)** that high-concentration THC cannabis products are associated with beneficial perceived health outcomes.

Sleep

Initial query of the evidence map resulted in 10 high- and two medium-relevancy studies addressing associations between the use of high-concentration THC products and sleep outcomes. After full manuscript review, eight studies were determined to be relevant to addressing the question of association of high-concentration THC cannabis products with sleep outcomes.

Of the relevant studies, four studied cannabis for its benefits, as a sleep aid.[26, 49, 50, 53] Two found statistically significant associations between high-concentration THC and beneficial sleep outcomes and two found no statistically significant associations.[26, 53] The populations included in those studies included participants with insomnia, chronic pain, glioma (growth near the spinal cord), or other medical cannabis use. These studies on medical cannabis use considered the sedative effects of THC to be beneficial in the context of their respective patient populations.

We conclude that there is a **Limited Amount of Evidence** (two statistically significant studies out of eight studies total**)** that high-concentration THC cannabis products are associated with beneficial sleep outcomes.

No Effect/Association

Cardiometabolic

Query of the evidence map identified nine studies that met the criteria for high-relevancy, and four for medium-relevancy in the category of Cardiometabolic outcomes, which includes such outcomes as heart rate and blood pressure. After full manuscript review, three studies were determined to be relevant.

All three studies described an increase in heart rate after both edible and flower cannabis use.[41, 60, 61] Bidwell et al. observed a more significant heart rate elevation after using flower cannabis compared with edible ingestion.[62] However, none of the studies performed a significance test for the association of THC concentration or dose with cardiometabolic outcomes. Based on these three studies there is some evidence that oral doses that were greater than 10 mg THC in adults can result in elevated heart rate without significant changes in blood pressure and that smoking cannabis increases heart rate more than ingestion (Note: the studies that examined these outcomes did not characterize them as adverse).

We conclude that there is **No Evidence** (no statistical testing among three studies) that high-concentration THC cannabis products are associated with cardiometabolic outcomes.

Gastrointestinal

Query of the evidence map found six studies that met the criteria of high-relevancy, and three for medium-relevancy in the category of Gastrointestinal outcomes. After full manuscript review, one study reported gastrointestinal outcomes comparing high-concentration products to low-concentration products and was deemed relevant.

Schloss et al. performed a randomized trial involving adult patients diagnosed with a high-grade glioma who received two different ratios of oral medicinal cannabis: oil-based organic whole plant extracts of cannabis based on a 1:1 and 4:1 ratio of THC:CBD (1:1 THC 4.6 mg/ml:CBD 4.8mg/ml and 4:1 THC 15mg/ml:CBD 3.8mg/ml).[26] There were no statistically significant differences in nausea between the treatment groups over 12 weeks of treatment.

We conclude that there is a **Limited Amount of Evidence** (one study that found no statistically significant associations).

Immunity

Only one paper was found in the evidence map that met the criteria and contained an outcome related to immunity. After full manuscript review, this one study was determined to be relevant.

Peters et al. tested five different doses of THC in a pharmacokinetic study and included adverse events sorted by various health outcomes.[36] Regarding immunity outcomes, only a single person from a single treatment reported any health outcome related to immunity. This study did not perform a formal statistical test to assess this association.

We conclude that there is **No Evidence** (no statistical testing in the one study) on the effect of high-concentration THC cannabis products on immunity related outcomes.

Ocular

Query of the evidence map resulted in two studies addressing associations between the use of high-concentration THC products and ocular outcomes. After full manuscript review, one study was determined to be relevant to addressing the question. In this study, there was a counterintuitive finding of the lowest dose of THC (5mg) being associated with increased intraocular pressure, in comparison to higher doses (10 mg and 15mg).[27] However, all values were in the normal range.

We conclude that there is a **Limited Amount of Evidence** (one study that found no statistically significant associations of one study total**).**

Respiratory

Query of the evidence map found six studies that address the association between high-concentration THC cannabis products and respiratory outcomes. After full-text review, two papers were found to be relevant. Peters et al. tested five different doses of THC and included adverse events sorted by various health outcomes.[36] There was no formal statistical test to assess the association between concentration or dose and respiratory outcomes. Prince et al. was a cross-sectional study that measured outcomes from 20% and 76% THC products.[52] Despite finding a weak correlation between overall concentration and outcome, the result was not statistically significant. There was, however, a statistically significant correlation between higher concentration used and higher frequency of use.

We conclude that there is a **Limited Amount of Evidence** (one study that had no statistically significant findings of two studies total**).**

Sexual and Reproductive Health Effects

The query of the evidence map resulted in one study addressing associations between the use of high-concentration THC products and sexual or reproductive health outcomes. The included study was a Phase 1 RCT that examined the safety and tolerability of Spectrum Red Softgels (2.5 mg THC).[36] Participants were randomized to five groups receiving 5, 10, 15, 20mg THC, or a placebo for seven days. Across all types of events, adverse effects were mild to moderate. As it relates to sexual and reproductive health, there were one to two events in some treatment groups of reproductive system and breast disorders, dysmenorrhea, and delayed menstruation. There were no tests of significant differences between treatment groups in the incidence of adverse events related to sexual and reproductive health.

We conclude that there is **No Evidence** (only one study without statistical significance testing) on effects of high-concentration THC cannabis products on sexual and reproductive health.

SPECIAL CONSIDERATION: HEALTH EFFECTS OF THC ON YOUNG CHILDREN

Respiratory Failure

Twelve case reports from the evidence map describe incidents of young children with exposure to high doses of THC. They show that such exposure can lead to coma and respiratory depression and, in some instances, a need for mechanical ventilation.[63-74] These effects appear most evident and strongly associated with edible products. These 12 studies, while case reports, are clear in showing that excessive doses of THC can depress respiration in large overdoses in young children. This conclusion is parallel to existing clinical literature on THC overdosage in children.[75-79]

PHARMACOKINETIC CONSIDERATIONS

In reaching overall conclusions based on the scientific literature identified for the four Policy Questions, we considered how Delta-9 Tetrahydrocannabinol (THC) is handled within the body. Like other ingested and inhaled substances, it is distributed throughout the body and undergoes metabolism. Through absorption, distribution, metabolism and excretion, THC concentration rises and falls after entering the body, affecting the amount of THC that reaches the key cannabinoid receptors in the brain. We briefly review that literature here to provide background for our findings in the scoping review and for supporting this report's recommendations.

THC is one of several phytocannabinoids found in Cannabis. It is known as the most psychoactive cannabinoid and concentrations vary in plants, not only among Cannabis species, but within commercially available forms. The two most common modalities of use include ingestion using tinctures or edible products, and inhalation via smoked or vaporized forms.

The modality of use and the characteristics of the product are key determinants of the effect of THC on users of cannabis products. The relationship between THC concentration (amount of THC) in a product and health outcomes is complex with several modifying factors. The physiological consequences of inhalation and ingestion of THC-containing products depend on the amount (dose) of THC reaching the cannabinoid receptors in the brain and other organs. The relationship of the biologically active dose reaching these receptors to the amount of THC entering the body (we refer to this as the "exposure dose") is complex (Table 4). Several factors influence the exposure dose after both acute and chronic use: route of administration, cannabis product THC concentration, duration, and frequency of use. An individual's tolerance influences end receptor regulation and signaling; impacting the amount of cannabis used and the physiologic effects in an individual. The more tolerant an individual is, the more THC is needed to achieve the same pharmacological effect.[80] In addition to cannabis product characteristics and use patterns, an individual's health characteristics will influence risk for the health outcomes. Individual health characteristics include age of initiation or use, preexisting health conditions, individual pharmacogenomics, i.e., the genes determining handling of the drug, and complex environmental and social factors.

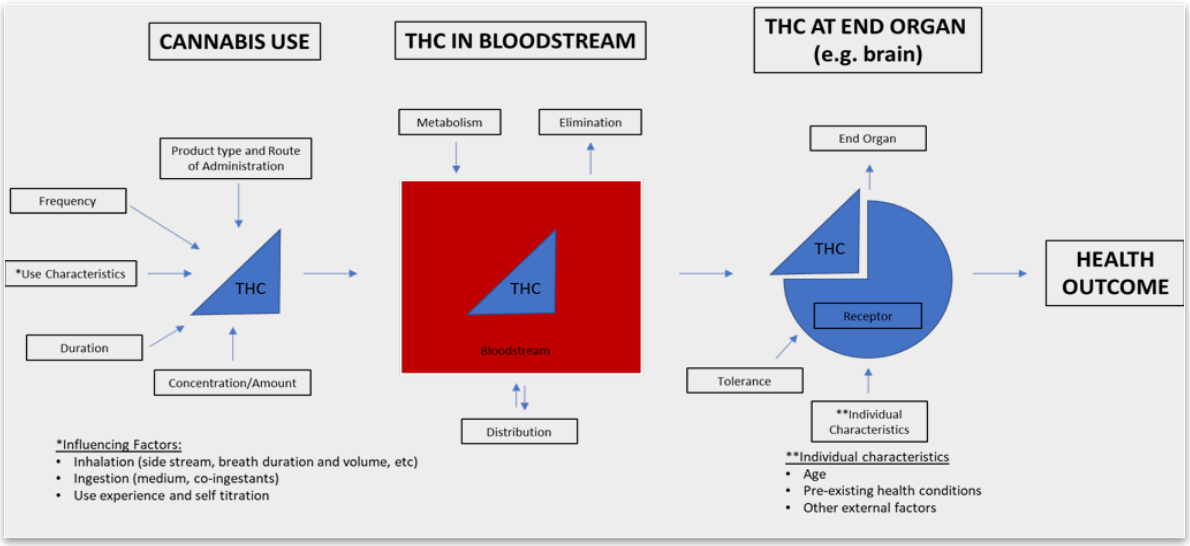
The pharmacokinetics (absorption, metabolism, distribution, and elimination) of THC and variables that can influence the pharmacokinetics plays a significant role in exposure dose (Table 5). The cannabis product and how it is used affect the bioavailability of THC, which is the proportion of THC that enters the blood circulation to have an active effect (Table 4). THC is metabolized by enzymes in the liver (mostly CYP2C and CYP3A).[81, 82] Both of these enzymes can have genetic variations on their activity level influencing how THC is metabolized and inactivated in the body. THC is lipophilic (can be stored in the fat in the body) and has a large volume of distribution, i.e., spreads throughout the body). These properties also lend themselves to slow time to equilibration and prolonged time to elimination (which occurs mostly in feces and urine).[81, 82]

However, one of the strongest influencing factors on exposure dose is the route of administration.[83] Ingestion of THC-containing products is associated with low bioavailability and slow absorption of THC.[81, 82, 84] Studies demonstrate a range of systemic bioavailability (how much of that ingested enters the circulation) showing that between 4-12% of THC is absorbed into the bloodstream after ingestion of cannabis. However, bioavailability can increase when taking the ingested product in a lipophilic medium (fat-containing), such as in baked goods, or in an oil formulation. THC is degraded by gastric acids, and there is extensive first pass metabolism in the liver (i.e., metabolism in the liver when the THC first enters the circulation), which further reduces the bioavailability.[85] Peak THC and metabolite concentrations are considerably lower than with inhaled routes of administration, with delayed time to peak concentration of two to four hours.

In contrast to ingestion, with inhaled forms of THC, detectable blood concentrations are found within seconds, with times to peak concentration within minutes.[81, 82, 86] Metabolites of THC can peak hours later with much longer times to elimination. Overall bioavailability of inhaled THC is higher than with oral forms (up to 50%) and it varies significantly with puff duration and volume (breath inhalation and hold), and form of inhalation. Pyrolysis, or burning, can destroy as much as 30% of THC product in addition to loss via sidestream emissions. Vaporization of cannabis can increase bioavailability by limiting the consequences of combustion, in addition to the use of high-concentration formulations[87, 88]. The experience of the user also influences these characteristics. Some evidence demonstrates “self-titration” of users when inhalational forms are used.[29, 62, 89] This concept proposes that regardless of the form (pyrolysis or vaping) and THC concentration of the product, users will self-regulate the amount of cannabis product they use to achieve the desired clinical effect. Experienced users will achieve the same peak THC concentration with a repeatable pattern of use.

These pharmacokinetic parameters in conjunction with variation in use patterns, chronicity of use, and “self-titration” can influence exposure dose in both acute and chronic timeframes. This complexity of self-dosing complicates linking one single determinant, e.g., concentration to risk for experiencing either a beneficial or adverse outcome. As previously stated, individual health characteristics also play a significant role in influencing health outcomes (Figure 6).

Figure 6: Factors influencing cannabis use and the flow of THC within the body.



From a public health perspective, there are limitations to what can be regulated in public consumption. There is no control over personal use patterns of frequency and chronicity of use, or modalities of use when all forms are allowed. However, regulations can incorporate age limitations, limit characteristics of available products, restrict THC concentration within various products, or provide limits on the amount purchased, all of which could reduce potential exposure dose of THC to an individual over time (Table 5, Figure 7).

Table 4: Key definitions related to the pharmacokinetics of THC.

Product concentration	**Percentage of THC in a cannabis product**
Exposure Dose	The relationship of the biologically active dose reaching end organ receptors to the amount of THC
Pharmacokinetics	How the drug is absorbed, distributed, metabolized, and eliminated in the body
Bioavailability	The proportion of THC enters the blood circulation to have an active effect

Table 5: Factors influencing dose including individual and product characteristics.

	Factors Influencing Exposure Dose	
	Individual Factors	Factors Modifiable by Regulations
Individual's Health Characteristics	x	
Frequency of Use	x	
Chronicity of Use	x	
Pattern of Use (puffs & self-titration)	x	

Cannabis Product Available (edible, smokeable, vaporized)		x
THC concentration/dose in a product (flower, concentrate, edible)		x
Age of legal use (age of initiation)		x
Maximum dose allowed in a time limit (Purchase limits)		x

Figure 7: Factors influencing THC exposure dose, including individual and product characteristics, that impact the health effects from use of high-concentration THC.

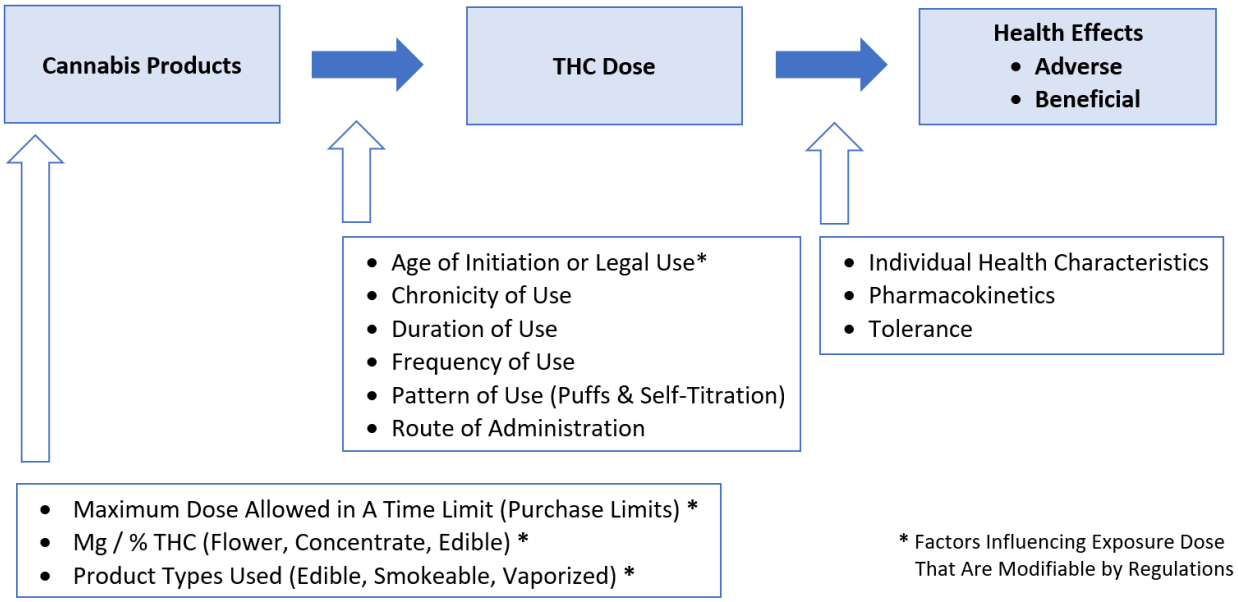


Figure 7 demonstrates the complexities in determining the THC exposure dose to an individual. Cannabis products refers to the product type used, maximum dose allowed in a time limit (purchase limits), and the concentration of THC in the product used. Many factors can influence the total amount of THC that is absorbed by an individual over time including the frequency, duration, and chronicity of use (including age of initiation), route of administration, and the pattern of use. The total exposure dose increases with chronicity of use, which may lead to more adverse health outcomes. The health effects from cannabis use constitute a multitude of factors that need to be included when determining the relationship between THC and health outcomes. Some of these factors are modifiable by regulation while others are isolated to the individual's use pattern, tolerance, and their own health characteristics.

CONCLUSIONS

This report provides the first full synthesis of the evidence on high-concentration marijuana and THC concentrates mandated by HB 1317. It reflects the work of a large multidisciplinary team that screened 66,234 scientific reports to identify the 452 studies covered here. The approach taken, carrying out a scoping review and using an evidence map to identify key studies, matched the heterogeneity of the literature, particularly the multiplicity of outcomes and diversity of approaches for assessing use of cannabis products. Additionally, for this pass through the 452 studies and to respond to the Colorado General Assembly expeditiously, this approach was appropriate.

The approach taken has inherent limitations, particularly when compared to carrying out multiple systematic reviews of specific questions. We have not yet completed full risk of bias assessments as would be done in a systematic review, although such reviews in the future will be complicated by the heterogeneity of the studies. The approach followed for synthesis—counting the number of studies available and tallying findings of those doing statistical significance testing—has limitations as well. The summary is qualitative and does not provide any information on the magnitude of effect and does not account for differences in study size or quality.[90] Considering statistical significance as a criterion can exclude studies that are underpowered to detect a clinically important effect; multiple studies could have identical effect sizes but all of the underpowered studies would be counted as 'no effect' in this method as a meta-analysis was not carried out.[91] Nevertheless, the combination of characterizing the amount of evidence available and providing a narrative summary can serve as the basis for using evidence for various outcomes, both adverse and beneficial, for decision-making.

The scoping review and evidence map do provide a comprehensive description of the literature on high-concentration THC marijuana and concentrates. The review does include a substantial number of reports of scientific investigations, but their utility for addressing the charge and intent of HB 1317 is diminished by the characteristics of the products investigated, the heterogeneity of approaches of included studies, and various methodological limitations of their designs. The review team has used the evidence map coupled with an organized review and classification of the findings to address the four policy-relevant questions derived with input from the Science Review Council. This report provides findings from this process for each of the four questions.

Table 6 provides a summary of the scope of evidence for the four Policy Questions. Reviewing the summaries, the limitations of the available evidence are clear. One critical problem for many of the outcomes is the limited scope of literature available. The evidence is classified as a **Moderate Amount** for only two of the outcomes while the rest are of a **Limited Amount** or completely lacking relevant studies. For some outcomes with the most abundant evidence, e.g., mental health, the diversity of outcomes, e.g., PTSD and ADHD, investigated poses a barrier to reaching certain conclusions.

Table 6: Conclusions by Policy Question and Outcome Domain.

Policy Question	Outcome Domain	Number of Statistically Significant Studies	Evidence Scope on Adverse Effects	Evidence Scope on Beneficial Effects
1. Are adolescents and young adults especially susceptible to adverse physical or mental health outcomes of high-concentration cannabis products?	Mental Health Conditions and Substance Use	2	**Limited** Amount of Evidence	-
2. Are individuals with preexisting mental health conditions especially susceptible to adverse mental health outcomes of high-concentration cannabis products?	Adverse Mental Health Outcomes	2	**Limited** Amount of Evidence	-
	Beneficial Applications for Mental Health Conditions	6	-	**Moderate** Amount of Evidence
3. Are pregnant and nursing women susceptible to adverse physical or mental health outcomes of high-concentration cannabis products? Are infants/children with prenatal and postnatal exposure to high-concentration cannabis products susceptible to adverse physical, neurodevelopmental or cognitive effects from this exposure?	Pre-, Peri-, and Neonatal	0	-	-
4. Are high-concentration THC cannabis products	Cancer Symptom Management	1	**Limited** Amount of Evidence	-

associated with greater risk of adverse physical or mental health outcomes than lower-concentration products? *	Driving Performance		3	**Limited** Amount of Evidence	-
	Mental Health		8	**Moderate** Amount of Evidence	-
			4	-	**Limited** Amount of Evidence
	Neurologic		1	**Limited** Amount of Evidence	-
			1	-	**Limited** Amount of Evidence
	Pain		2	-	**Limited** Amount of Evidence
	Per-, Peri-, and Neonatal		0	-	-
	Pregnancy		0	-	-
	Psychosocial		1	**Limited** Amount of Evidence	-
	Sleep		1	**Limited** Amount of Evidence	-
			2	-	**Limited** Amount of Evidence
	Substance Use / Substance Dependence		1	**Limited** Amount of Evidence	-
	Other	Dry Mouth	1	**Limited** Amount of Evidence	-
		Perceived Health	2	-	**Limited** Amount of Evidence

Note: To capture the scope of the evidence, a scale was created for the amount of the available evidence based on the number of statistically significant studies. The numbers of studies are classified as: none, limited (1-4), moderate (5-9), and substantial (10+).

***** In reference to Policy Question 4, the following outcome domains: cardiometabolic (n=3), gastrointestinal (n=1), immunity (n=1), ocular (n=1), respiratory (n=2), and sexual and reproductive health effects (n=1) did not provide sufficient data to rate conclusions because either no statistical tests were performed, or no statistical associations were found.

Beyond the findings for the four Policy Questions, the scoping review provides critical over-arching findings with regard to the state of the evidence:

- From the outset of this review, we found the scientific research focusing on high-concentration cannabis to be limited, particularly in its relevance to the products available today (see Figures 1 and 2). The numbers of studies addressing products at today's concentrations are limited. Thus, the generalizability of the accumulated scientific evidence is critically limited for addressing questions about today's marketplace.

- Overall, methodological limitations of the studies are a barrier to applying their findings. Limitations in research methods reflect the practical difficulties in doing research on cannabis, restricted funding, lack of standardized methods for assessing exposure, and the wide range of outcomes studied using experimental and observational approaches.

- As to Policy Question 4, whether high-concentration products pose a greater risk for adverse outcomes, there is evidence for mental and behavioral health outcomes. We did conclude that there is a **Moderate Amount of Evidence** (eight statistically significant studies of 19 total studies) that high-concentration THC cannabis products are associated with adverse mental health outcomes for those with preexisting mental health conditions.

- As to Policy Question 2, there was evidence that high-concentration THC cannabis products have been associated with beneficial outcomes in those with pre-existing mental health conditions. We found that there is **Moderate Amount of Evidence** (six statistically significant studies of 15 total studies) that high-concentration THC cannabis products are associated with beneficial outcomes for those with a range of preexisting mental health conditions. However, for any of the specific mental health conditions, the number of studies was limited.

- The evidence reviewed does not provide an accurate picture of how risk for adverse outcomes varies with concentration or other indicators of THC dose. That is, the literature is not sufficiently robust to determine, for example, if risks increase only above some threshold level of concentration (or dose) or if risks increase with increasing concentration without a threshold. Considering the wide range of products and patterns of use, the pharmacokinetics of THC and the phenomenon of tolerance, there is not a strong basis for anticipating that thresholds can be identified for THC concentration that might be useful for informing product safety standards.

We end with comments on the limitations of the evidence review described in this report. Under HB 1317, the Colorado School of Public Health was given a specific charge related to high-concentration marijuana and THC concentrates. The review was targeted by design to that question. Thus, we did not review the full scope of the scientific literature on cannabis use, covering all potential harms and benefits. The review by the Colorado School of Public Health did not have the purpose of reaching any conclusions on the broad impact of legalized access to cannabis and THC-containing products for recreational purposes.

Note: We offer the reminder that this is a focused review on questions related to the charge given to the ColoradoSPH by HB 1317. It is not a general review of the broad scope of issues related to public health and to beneficial/medical uses of cannabis and THC. Rather, the focus is "…on physical and mental health effects of **high-potency** THC marijuana and concentrates," per the charge to the committee. For those seeking information on marijuana and concentrates generally, there are general resources available, such as the CDC's Marijuana and Public Health page and NIDA's Cannabis (Marijuana) DrugFacts page. This report and the scope of our work under the charge of HB 1317 do not address cannabinoids other than THC.

RECOMMENDATIONS

- Some of the problems of the scientific literature on cannabis have been recognized; they need to be addressed so that future research is more informative. In particular, standardized approaches are needed for characterizing the use of cannabis products to assure comparability among studies. These approaches need to be modified in a timely way so that the instruments used for research reflect patterns of use. Systematic reviews and meta-analyses would be facilitated by such standardization. Attention to use of common methods for outcome assessment in studies of cannabis would be similarly valuable.

- We are preparing a commentary on these problems for publication in the scientific literature. Advances in methodology could be made by convening researchers and research funders to develop standardized approaches, as done for other environmental agents, e.g., tobacco products.

- Following input from the Scientific Review Council, we plan to complete systematic reviews related to mental health outcomes.

- With funding from the State of Colorado, a valuable resource that will be publicly available has been developed for public health and scientific purposes. To our knowledge, the scoping review and evidence map are unique. We recommend sustained support to continually update this resource, given the rapid growth of the scientific

literature, the growing availability of recreational and medical cannabis, and the availability of high-concentration products.

EDUCATION CAMPAIGN UPDATE

An interim report of the campaign is provided below. The health education campaign team is working on multiple activities:

1. An overview of reviews of health communication campaigns to identify the best practices and most effective strategies that have been used over time to impact health behavior and reduce behaviors that increase risk for poor health outcomes.

We have completed the titles/abstracts (655 studies) and full-text screening (149 studies) that show positive evidence on knowledge or awareness of health and risky behavior, attitudes, beliefs, opinions, and norms related to health behaviors and health outcomes from health education campaigns. stages and have designed and piloted the data extraction form. We now have 70 studies to extract as the next part of the process.

This review will be completed by the end of May 2023 and will offer guidance on strategies we should consider in generating an effective education campaign.

2. A descriptive review of the use of 21st Century media strategies for reaching and communicating with diverse audiences (e.g., social media, text messaging, Web Logs (Blogs)

We have identified 8,373 descriptive studies and have screened 3,394 studies to review that have successfully delivered health education and healthy behavior campaigns using the internet, social media and text messaging to document strategies that effectively identify, reach, and engage diverse audiences with health campaign messaging.

This review will be complete by the end of May 2023 and will offer ideas for how we may best reach large numbers of Coloradans via 21st Century communication strategies with our messaging about the impacts of high-concentration marijuana use.

3. Convene an adult and a youth advisory group comprising diverse audiences across Colorado to offer perspective on the types of messages we can share and to react to vendors who propose health communication campaigns.

To date, we have convened a group of four community liaisons who are working with us to identify and convene the adult community advisors and the youth community advisors. The liaisons represent diverse communities across Colorado, including communities experiencing

mental illness, rural communities, communities of color, and LGBTQI+ communities. We are in the process of inviting community advisors to an inaugural meeting planned for early March.

4. Identifying key messages to share and key audiences to reach through the health education campaign. With information from the research reviews (including the systematic review on health impacts of high-concentration marijuana), and input and perspectives from diverse community members across the state we will work to identify key messages to share through our health education activities. We will also establish priority audiences for health education campaigns.

5. Identifying vendors who have potential for the design and delivery of effective campaigns for diverse priority audiences related to the health impacts of high-concentration marijuana use. With information from the research reviews (including the systematic review on health impacts of high-concentration marijuana), and input and perspectives from diverse community members across the state we will work to identify vendors who have potential to design and deliver engaging and compelling health education messaging related to the impacts of high-concentration marijuana consumption.

Following is a table depicting the specific deliverables and timeline for the education campaign team activities (Table 7).

Table 7: Summary of educational campaign activities.

Activity	**Timeline—*ON TRACK***	**Deliverable**
Overview of systematic reviews	Complete By May 2023-***In Progress***	Summary of evidence-based strategies that have been impactful in facilitation of healthy behavior or reduction of health risk behavior
Descriptive review of 21st Century communication strategies	Complete by May 2023-***In Progress***	Summary of strategies that have been tried to improve reach and engagement of diverse audiences using social media and technology-based modalities

Convene community advisory groups	Initial meetings begin January 2023 and continue through June 2023-***Ongoing***	Summary of diverse perspectives on proposed health education message content; identification of potential vendors who could effectively craft and delivery health education messaging
Identify key message content for education campaigns on the impact of high-concentration marijuana consumption	Complete by April 2023	A list of critical message content to include in health education campaigns; potentially include three to five key messages
Identify priority audiences to receive campaign content	Complete by January 2023-***COMPLETED***	Identify initial groups who are priority audiences to receive health education messaging
Identify vendors with potential to generate compelling health education content	Complete by June 2023	Identify three to five vendors who have potential to generate compelling health education content

REFERENCES

1. National Institute on Drug Abuse. Cannabis (Marijuana) Potency. Updated November 23, 2022. Accessed April 6, 2023. https://nida.nih.gov/research-topics/marijuana/cannabis-marijuana-potency
2. MPG Consulting, Business UoC-BLSo. *2020 Regulated Marijuana Market Update, Prepared for: Colorado Department of Revenue, Marijuana Enforcement Division* 2020.
3. Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *bmj*. 2020;368
4. Leventhal AM, Bae D, Kechter A, Barrington-Trimis JL. Psychiatric comorbidity in adolescent use and poly-use of combustible, vaporized, and edible cannabis products. *Journal of psychiatric research*. 2020;124:91-98.
5. Hines LA, Freeman TP, Gage SH, et al. Association of High-Potency Cannabis Use With Mental Health and Substance Use in Adolescence. *JAMA Psychiatry*. Oct 1 2020;77(10):1044-1051. doi:https://dx.doi.org/10.1001/jamapsychiatry.2020.103510.1001/jamapsychiatry.2020.1035 .
6. Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *The Lancet Psychiatry*. 2019;6(5):427-436.
7. Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *The Lancet Psychiatry*. 2015;2(3):233-238.
8. Di Forti M, Sallis H, Allegri F, et al. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia bulletin*. 2014;40(6):1509-1517.
9. Di Forti M, Morgan C, Dazzan P, et al. High-potency cannabis and the risk of psychosis. *The British Journal of Psychiatry*. 2009;195(6):488-491.
10. Sami M, Quattrone D, Ferraro L, et al. Association of extent of cannabis use and psychotic like intoxication experiences in a multi-national sample of first episode psychosis patients and controls. *Psychological medicine*. 2021;51(12):2074-2082.
11. Quattrone D, Ferraro L, Tripoli G, et al. Daily use of high-potency cannabis is associated with more positive symptoms in first-episode psychosis patients: the EU-GEI case–control study. *Psychological medicine*. 2021;51(8):1329-1337.
12. Sideli L, Fisher HL, Murray RM, et al. Interaction between cannabis consumption and childhood abuse in psychotic disorders: preliminary findings on the role of different patterns of cannabis use. *Early intervention in Psychiatry*. 2018;12(2):135-142.
13. Schoeler T, Petros N, Di Forti M, et al. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. *The Lancet Psychiatry*. 2016/10/01/ 2016;3(10):947-953. doi:https://doi.org/10.1016/S2215-0366(16)30188-2
14. Madero S, Oliveras C, Pons M, et al. Cannabis use the week before admission to psychiatric in-patient service as a marker of severity. *Journal of psychiatric research*. 2020;129:40-46.
15. Shelef A, Barak Y, Berger U, et al. Safety and efficacy of medical cannabis oil for behavioral and psychological symptoms of dementia: an-open label, add-on, pilot study. *Journal of Alzheimer's disease*. 2016;51(1):15-19.

16. Matsumoto T, Kawabata T, Okita K, et al. Risk factors for the onset of dependence and chronic psychosis due to cannabis use: Survey of patients with cannabis-related psychiatric disorders. *Neuropsychopharmacology reports*. 2020;40(4):332-341.
17. Kayser RR, Haney M, Raskin M, Arout C, Simpson HB. Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: A human laboratory study. *Depression and anxiety*. 2020;37(8):801-811.
18. Mauzay D, LaFrance EM, Cuttler C. Acute Effects of Cannabis on Symptoms of Obsessive-Compulsive Disorder. *J Affect Disord*. Jan 15 2021;279:158-163. doi:https://dx.doi.org/10.1016/j.jad.2020.09.12410.1016/j.jad.2020.09.124. Epub 2020 Oct 6.
19. Casarett DJ, Beliveau JN, Arbus MS. Benefit of Tetrahydrocannabinol versus Cannabidiol for Common Palliative Care Symptoms. *J Palliat Med*. Oct 2019;22(10):1180-1184. Comment in: J Palliat Med. 2019 Nov;22(11):1301; PMID: 31661397 [https://www.ncbi.nlm.nih.gov/pubmed/31661397]. doi:https://dx.doi.org/10.1089/jpm.2018.065810.1089/jpm.2018.0658. Epub 2019 Aug 6.
20. Hergenrather JY, Aviram J, Vysotski Y, Campisi-Pinto S, Lewitus GM, Meiri D. Cannabinoid and terpenoid doses are associated with adult ADHD status of medical cannabis patients. *Rambam Maimonides Medical Journal*. 2020;11(1)
21. LaFrance EM, Glodosky NC, Bonn-Miller M, Cuttler C. Short and long-term effects of cannabis on symptoms of post-traumatic stress disorder. *Journal of affective disorders*. 2020;274:298-304.
22. Bonn-Miller MO, Sisley S, Riggs P, et al. The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial. *PloS one*. 2021;16(3):e0246990.
23. Stith SS, Li X, Diviant JP, et al. The effectiveness of inhaled Cannabis flower for the treatment of agitation/irritability, anxiety, and common stress. *Journal of Cannabis Research*. 2020;2(1):1-14.
24. Li X, Diviant JP, Stith SS, et al. Focus: Plant-based Medicine and Pharmacology: The Effectiveness of Cannabis Flower for Immediate Relief from Symptoms of Depression. *The Yale Journal of Biology and Medicine*. 2020;93(2):251.
25. Cuttler C, Spradlin A, McLaughlin RJ. A naturalistic examination of the perceived effects of cannabis on negative affect. *Journal of affective disorders*. 2018;235:198-205.
26. Schloss J, Lacey J, Sinclair J, et al. A Phase 2 Randomised Clinical Trial Assessing the Tolerability of Two Different Ratios of Medicinal Cannabis in Patients With High Grade Gliomas. *Front Oncol*. 2021;11:649555. doi:https://dx.doi.org/10.3389/fonc.2021.6495510.3389/fonc.2021.649555. eCollection 2021.
27. Levitt M, Wilson A, Bowman D, et al. Physiologic observations in a controlled clinical trial of the antiemetic effectiveness of 5, 10, and 15 mg of delta 9-tetrahydrocannabinol in cancer chemotherapy. Ophthalmologic implications. *Journal of clinical pharmacology*. 1981;21(S1):103S-109S.
28. Lopez-Pelayo H, Campeny E, Oliveras C, et al. Early, Chronic, and Acute Cannabis Exposure and Their Relationship With Cognitive and Behavioral Harms. *Front Psychiatry*. 2021;12:643556.

doi:https://dx.doi.org/10.3389/fpsyt.2021.64355610.3389/fpsyt.2021.643556. eCollection 2021.

29. Marcotte TD, Umlauf A, Grelotti DJ, et al. Driving Performance and Cannabis Users' Perception of Safety: A Randomized Clinical Trial. *JAMA Psychiatry*. Mar 1 2022;79(3):201-209. doi:10.1001/jamapsychiatry.2021.4037
30. Lenne MG, Dietze PM, Triggs TJ, Walmsley S, Murphy B, Redman JR. The effects of cannabis and alcohol on simulated arterial driving: Influences of driving experience and task demand. *Accid Anal Prev*. May 2010;42(3):859-66. doi:https://dx.doi.org/10.1016/j.aap.2009.04.02110.1016/j.aap.2009.04.021.
31. Ronen A, Gershon P, Drobiner H, et al. Effects of THC on driving performance, physiological state and subjective feelings relative to alcohol. *Accid Anal Prev*. May 2008;40(3):926-34. doi:https://dx.doi.org/10.1016/j.aap.2007.10.01110.1016/j.aap.2007.10.011. Epub 2007 Nov 26.
32. Hartley S, Simon N, Larabi A, et al. Effect of Smoked Cannabis on Vigilance and Accident Risk Using Simulated Driving in Occasional and Chronic Users and the Pharmacokinetic-Pharmacodynamic Relationship. *Clin Chem*. May 2019;65(5):684-693. doi:https://dx.doi.org/10.1373/clinchem.2018.29972710.1373/clinchem.2018.299727. Epub 2019 Mar 14.
33. Rafaelsen OJ, Bech P, Christiansen J, Christrup H, Nyboe J, Rafaelsen L. Cannabis and alcohol: effects on stimulated car driving. *Science*. Mar 2 1973;179(4076):920-3. doi:https://dx.doi.org/10.1126/science.179.4076.92010.1126/science.179.4076.920.
34. Noyes R, Jr B, S. F B, D. A C. Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol*. Feb-Mar 1975;15(2-3):139-43. doi:https://dx.doi.org/10.1002/j.1552-4604.1975.tb02348.x10.1002/j.1552-4604.1975.tb02348.x.
35. Wan BA, Diaz P, Blake A, et al. Efficacy of different varieties of medical cannabis in relieving symptoms. Article. *Journal of Pain Management*. 2017;10(4):375-383.
36. Peters EN, Mosesova I, MacNair L, et al. Safety, Pharmacokinetics and Pharmacodynamics of Spectrum Red Softgels in Healthy Participants. Randomized Controlled Trial. *Journal of Analytical Toxicology*. 2022;46(5):528-539.
37. Prince MA, Conner BT. Examining links between cannabis potency and mental and physical health outcomes. *Behaviour Research and Therapy*. 2019;115:111-120.
38. Steeger CM, Hitchcock LN, Bryan AD, Hutchison KE, Hill KG, Bidwell LC. Associations between self-reported cannabis use frequency, potency, and cannabis/health metrics. *Int J Drug Policy*. Nov 2021;97:103278. doi:https://dx.doi.org/10.1016/j.drugpo.2021.10327810.1016/j.drugpo.2021.103278. Epub 2021 May 30.
39. Drennan ML, Karoly HC, Bryan AD, Hutchison KE, Bidwell LC. Acute objective and subjective intoxication effects of legal-market high potency THC-dominant versus CBD-dominant cannabis concentrates. Article. *Scientific reports*. 2021;11(1):21744. doi:10.1038/s41598-021-01128-2

40. Brunt TM, van Genugten M, Honer-Snoeken K, van de Velde MJ, Niesink RJ. Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. *J Clin Psychopharmacol*. Jun 2014;34(3):344-9. doi:https://dx.doi.org/10.1097/JCP.000000000000012910.1097/JCP.0000000000000129.

41. Schlienz NJ, Spindle TR, Cone EJ, et al. Pharmacodynamic dose effects of oral cannabis ingestion in healthy adults who infrequently use cannabis. *Drug Alcohol Depend*. Mar 21 2020;211:107969. doi:https://dx.doi.org/10.1016/j.drugalcdep.2020.1079610.1016/j.drugalcdep.2020.107969.

42. Sainz-Cort A, Jimenez-Garrido D, Munoz-Marron E, Viejo-Sobera R, Heeroma J, Bouso JC. Opposite Roles for Cannabidiol and delta-9-Tetrahydrocannabinol in Psychotomimetic Effects of Cannabis Extracts: A Naturalistic Controlled Study. *J Clin Psychopharmacol*. Sep-Oct 01 2021;41(5):561-570. doi:https://dx.doi.org/10.1097/JCP.000000000000145710.1097/JCP.0000000000001457.

43. Mueller RL, Ellingson JM, Bidwell LC, Bryan AD, Hutchison KE. Are the Acute Effects of THC Different in Aging Adults? *Brain Sci*. May 1 2021;11(5)doi:https://dx.doi.org/10.3390/brainsci1105059010.3390/brainsci11050590.

44. Wildes M, Bigand TL, Layton ME, Wilson M. Cannabis Use and Cognition in Adults Prescribed Opioids for Persistent Pain. *Pain Manag Nurs*. Feb 2020;21(1):94-99. doi:https://dx.doi.org/10.1016/j.pmn.2019.06.01410.1016/j.pmn.2019.06.014. Epub 2019 Aug 9.

45. Hunault CC, Bocker KB, Stellato RK, Kenemans JL, e Vries I, Meulenbelt J. Acute subjective effects after smoking joints containing up to 69 mg Delta9-tetrahydrocannabinol in recreational users: a randomized, crossover clinical trial. *Psychopharmacology (Berl)*. Dec 2014;231(24):4723-33. doi:https://dx.doi.org/10.1007/s00213-014-3630-210.1007/s00213-014-3630-2. Epub 2014 May 31.

46. Taylor SP, Vardaris RM, Rawtich AB. The effects of alcohol and delta 9 tetrahydrocannabinol on human physical aggression. *Aggressive Behavior*. 1976;2(2):153-161.

47. Weinstein A, Brickner O, Lerman H, et al. A study investigating the acute dose-response effects of 13 mg and 17 mg Delta 9- tetrahydrocannabinol on cognitive-motor skills, subjective and autonomic measures in regular users of marijuana. *J Psychopharmacol*. Jun 2008;22(4):441-51. doi:https://dx.doi.org/10.1177/0269881108088194.10.1177/0269881108088194.

48. Gustavsen S, Hb S, K L, et al. Safety and efficacy of low-dose medical cannabis oils in multiple sclerosis. *Mult Scler Relat Disord*. Feb 2021;48:102708. doi:https://dx.doi.org/10.1016/j.msard.2020.10270810.1016/j.msard.2020.102708. Epub 2020 Dec 30.

49. Winiger EA, Hitchcock LN, Bryan AD, Bidwell LC. Cannabis use and sleep: expectations, outcomes, and the role of age. *Addictive behaviors*. 2021;112:106642.

50. Sznitman SR, Vulfsons S, Meiri D, Weinstein G. Medical cannabis and insomnia in older adults with chronic pain: a cross-sectional study. *BMJ supportive & palliative care*. 2020;10(4):415-420.

51. Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of Delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol*. Jun 2004;24(3):305-13. doi:https://dx.doi.org/10.1097/01.jcp.0000125688.05091.8f10.1097/01.jcp.0000125688.05091.8f.

52. Prince MA, Conner BT. Examining links between cannabis potency and mental and physical health outcomes. *Behav Res Ther*. Apr 2019;115:111-120. doi:https://dx.doi.org/10.1016/j.brat.2018.11.00810.1016/j.brat.2018.11.008. Epub 2018 Nov 17.

53. Cousens K, DiMascio A. (-) Delta 9 THC as an hypnotic. An experimental study of three dose levels. *Psychopharmacologia*. 1973;33(4):355-64.
54. S G, Hb S, K L, et al. Safety and efficacy of low-dose medical cannabis oils in multiple sclerosis. *Mult Scler Relat Disord*. Feb 2021;48:102708. doi:https://dx.doi.org/10.1016/j.msard.2020.10270810.1016/j.msard.2020.102708. Epub 2020 Dec 30.

55. Li X, Diviant JP, Stith SS, et al. The Effectiveness of Cannabis Flower for Immediate Relief from Symptoms of Depression. *Yale J Biol Med*. Jun 2020;93(2):251-264.
56. Mauzay D, LaFrance EM, Cuttler C. Acute effects of cannabis on symptoms of obsessive-compulsive disorder. *Journal of Affective Disorders*. 2021;279:158-163.
57. Stith SS, Vigil JM, Brockelman F, Keeling K, Hall B. The Association between Cannabis Product Characteristics and Symptom Relief. *Sci Rep*. Feb 25 2019;9(1):2712. doi:https://dx.doi.org/10.1038/s41598-019-39462-110.1038/s41598-019-39462-1.

58. Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. *Adv Alcohol Subst Abuse*. 1987;7(1):39-50. doi:https://dx.doi.org/10.1300/j251v07n01_0410.1300/j251v07n01_04.

59. Stith SS, Diviant JP, Brockelman F, et al. Alleviative effects of Cannabis flower on migraine and headache. *J Integr Med*. Sep 2020;18(5):416-424. doi:https://dx.doi.org/10.1016/j.joim.2020.07.00410.1016/j.joim.2020.07.004. Epub 2020 Jul 18.

60. Karniol IG, Shirakawa I, Takahashi RN, Knobel E, Musty RE. Effects of delta9-tetrahydrocannabinol and cannabinol in man. *Pharmacology*. 1975;13(6):502-12. doi:https://dx.doi.org/10.1159/00013694410.1159/000136944.

61. Bidwell LC, Ellingson JM, Karoly HC, et al. Association of naturalistic administration of cannabis flower and concentrates with intoxication and impairment. *JAMA psychiatry*. 2020;77(8):787-796.
62. Bidwell LC, Karoly HC, Torres MO, Master A, Bryan AD, Hutchison KE. A naturalistic study of orally administered vs. inhaled legal market cannabis: cannabinoids exposure, intoxication, and impairment. *Psychopharmacology*. 2022;239(2):385-397.
63. Noble MJ, Hedberg K, Hendrickson RG. Acute cannabis toxicity. *Clinical toxicology*. 2019;57(8):735-742.
64. Pettinger G, Duggan M, Forrest A. Black stuff and babies. Accidental ingestion of cannabis resin. *Medicine, Science and the Law*. 1988;28(4):310-311.

65. Kaczor EE, Mathews B, LaBarge K, Chapman BP, Carreiro S. Cannabis product ingestions in pediatric patients: ranges of exposure, effects, and outcomes. *Journal of medical toxicology*. 2021;17(4):386-396.
66. Mattimoe C, Conlon E, Ni Siochain D. Edible cannabis toxicity in young children: an emergent serious public health threat. *Irish Med J*. 2021;114(8):446.
67. Macnab A, Anderson E, Susak L. Ingestion of cannabis: a cause of coma in children. *Pediatric emergency care*. 1989;5(4):238-239.
68. Gilbert JD, Grabowski M, Byard RW. Intravenous administration of cannabis and lethal anaphylaxis. *Medicine, Science and the Law*. 2017;57(2):91-94.
69. Heizer JW, Borgelt LM, Bashqoy F, Wang GS, Reiter PD. Marijuana misadventures in children: exploration of a dose-response relationship and summary of clinical effects and outcomes. *Pediatric Emergency Care*. 2018;34(7):457-462.
70. Chartier C, Penouil F, Blanc-Brisset I, Pion C, Descatha A, Deguigne M. Pediatric cannabis poisonings in France: more and more frequent and severe. *Clinical toxicology*. 2021;59(4):326-333.
71. Wang G, Roosevelt G, Heard K. Pediatric marijuana exposures in a medical marijuana state *JAMA Pediatr*. 2013;167(7):630-633.
72. Akpunonu P, Baum RA, Reckers A, et al. Sedation and acute encephalopathy in a pediatric patient following ingestion of delta-8-tetrahydrocannabinol gummies. *The American Journal of Case Reports*. 2021;22:e933488-1.
73. Lwin TS, Mitrakrishnan RN, Farooq M, Alama M. ST-segment elevation myocardial infarction with normal coronary arteries secondary to anterior communicating cerebral artery aneurysmal rupture: a case report. *European Heart Journal-Case Reports*. 2021;5(5):ytab168.
74. Mehamha H, Doudka N, Minodier P, et al. Unintentional cannabis poisoning in toddlers: A one year study in Marseille. *Forensic science international*. 2021;325:110858.
75. Leubitz A, Spiller HA, Jolliff H, Casavant M. Prevalence and clinical characteristics of unintentional ingestion of marijuana in children younger than 6 years in states with and without legalized marijuana laws. *Pediatric Emergency Care*. 2021;37(12):e969-e973.
76. Bennett CE, Venkataramani A, Henretig FM, Faerber J, Song L, Wood JN. Recent trends in marijuana-related hospital encounters in young children. *Academic pediatrics*. 2022;22(4):592-597.
77. Cohen N, Galvis Blanco L, Davis A, et al. Pediatric cannabis intoxication trends in the pre and post-legalization era. *Clinical Toxicology*. 2022/01/02 2022;60(1):53-58. doi:10.1080/15563650.2021.1939881
78. Leonard JB, Laudone T, Hines EQ, Klein-Schwartz W. Critical care interventions in children aged 6 months to 12 years admitted to the pediatric intensive care unit after unintentional cannabis exposures. *Clinical Toxicology*. 2022;60(8):960-965.
79. Tweet MS, Nemanich A, Wahl M. Pediatric Edible Cannabis Exposures and Acute Toxicity: 2017–2021. *Pediatrics*. 2023;
80. Lee D, Bergamaschi MM, Milman G, et al. Plasma Cannabinoid Pharmacokinetics After Controlled Smoking and Ad libitum Cannabis Smoking in Chronic Frequent Users. *J Anal Toxicol*. Oct 2015;39(8):580-7. doi:10.1093/jat/bkv082
81. Huestis MA. Pharmacokinetics and metabolism of the plant cannabinoids, delta9-tetrahydrocannabinol, cannabidiol and cannabinol. *Handb Exp Pharmacol*. 2005;(168):657-90. doi:10.1007/3-540-26573-2_23

82. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42(4):327-60. doi:10.2165/00003088-200342040-00003
83. Swortwood MJ, Newmeyer MN, Andersson M, Abulseoud OA, Scheidweiler KB, Huestis MA. Cannabinoid disposition in oral fluid after controlled smoked, vaporized, and oral cannabis administration. *Drug Test Anal*. Jun 2017;9(6):905-915. doi:10.1002/dta.2092
84. Vandrey R, Herrmann ES, Mitchell JM, et al. Pharmacokinetic Profile of Oral Cannabis in Humans: Blood and Oral Fluid Disposition and Relation to Pharmacodynamic Outcomes. *J Anal Toxicol*. Mar 1 2017;41(2):83-99. doi:10.1093/jat/bkx012
85. Bar-Hai A, Domb AJ, Hoffman A. Strategies for enhancing the oral bioavailability of cannabinoids. *Expert Opin Drug Metab Toxicol*. May 2022;18(5):313-322. doi:10.1080/17425255.2022.2099837
86. Carli R. [Behavior and clinical significance of factor VII in gynecology and obstetrics]. *Arch Med Interna*. Jan-Feb 1956;8(1):13-26. Comportamento e significato clinico del fattore VII in ginecologia e in ostetricia.
87. Spindle TR, Cone EJ, Schlienz NJ, et al. Acute Effects of Smoked and Vaporized Cannabis in Healthy Adults Who Infrequently Use Cannabis: A Crossover Trial. *JAMA Netw Open*. Nov 2 2018;1(7):e184841. doi:10.1001/jamanetworkopen.2018.4841
88. Spindle TR, Cone EJ, Schlienz NJ, et al. Acute Pharmacokinetic Profile of Smoked and Vaporized Cannabis in Human Blood and Oral Fluid. *J Anal Toxicol*. May 1 2019;43(4):233-258. doi:10.1093/jat/bky104
89. Leung J, Stjepanović D, Dawson D, Hall WD. Do Cannabis Users Reduce Their THC Dosages When Using More Potent Cannabis Products? A Review. *Front Psychiatry*. 2021;12:630602. doi:10.3389/fpsyt.2021.630602
90. Borenstein MH, L.V. Higgins, J.P.T. Rothstein, H.R. Meta-Analysis Methods Based on Direction and p-Values. In: M. Borenstein, L.V. Hedges, J.P.T. Higgins, Rothstein HR, eds. *Introduction to Meta-Analysis*. 2009:325-330.
91. Hedges LV, Vevea JL. Fixed- and Random-Effects Models in Meta-Analysis. *Psychological Methods*. 1998;3(4):486-504. doi:https://doi.org/10.1037/1082-989X.3.4.486

APPENDIX

Appendix Table 1: Scientific Review Council Members

Member	Role on Council per HB 21-1317	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 with experience recommending medical marijuana 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

Appendix Table 2: Cannabis Research & Policy Project Team Members

Member	Sub-Team
Lisa Bero, PhD	Systematic Review
Paige Buchanan-Hall, BA	Educational Campaign
Sheana Bull, PhD, MPH	Educational Campaign
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
Tsz Wing Yim, MPH	Systematic Review

We thank the Colorado School of Public Health graduate students for their work in screening studies and extracting data.

Appendix Table 3: Studies excluded from analysis by exclusion criteria.

Policy Question One: Are adolescents and young adults especially susceptible to adverse physical or mental health outcomes of high-concentration cannabis products?

Exclusion Criteria Hierarchy	N =	Citation
No data provided to show association between THC and health effects	10	Ogourtsova et al., 2018[1]; Stevens et al., 2021[2]; Braymiller et al., 2020[3]; Hoffenberg et al., 2019[4]; Morgan et al., 2018[5]; Case et al., 2022[6]; Mackie et al., 2021[7]; Stevens et al., 2021[8]; Audrain-McGovern et al., 2018[9]; Gunn et al., 2020[10]
Did not include population of interest	3	Fares et al., 2021[11]; Sznitman et al., 2020[12]; Parks et al., 2022[13].
Below THC concentration of interest threshold (<5mg or <10% THC)	3	Tennant et al., 1971[14]; Makela et al., 2006[15]; Greenberg et al., 1976[16]
Insufficient data on concentration, frequency, or duration	0	-

Appendix Table 4: Studies excluded from analysis by exclusion criteria

Policy Question Two: Are individuals with preexisting mental health conditions more susceptible to adverse mental health outcomes of high-concentration cannabis products?

Exclusion Criteria Hierarchy	N =	Citation
No data provided to show association between THC and health effects	10	Winiger et al., 2021[17]; Ferraro et al., 2013[18]; Roitman et al., 2014[19]; Kayser et al., 2021[20]; Matsumoto et al., 2020[21]; Smith et al., 2017[22]; Bonn-Miller et al., 2022[23]; Sakal et al., 2022[24]; Ferraro et al., 2019[25] , Drost et al., 2017[26]
Did not contain population of interest	2	Martin-Santos et al., 2012[27]; Bidwell et al., 2020[28]
Below THC concentration of interest threshold (<5mg or <10% THC)	1	D'Souza et al., 2005[29]
Insufficient data on concentration, frequency, or duration	6	Sideli et al., 2018[30]; Schoeler et al., 2016[31]; Bianconi et al., 2016[32]; Barrowclough et al., 2015[33]; Martin et al., 2021[34]; Kuhathasan et al., 2022[35]

Appendix Table 5: Studies excluded from analysis by exclusion criteria

Policy Question Three: Are pregnant and nursing women susceptible to adverse physical or mental health outcomes of high-concentration cannabis products? Are infants/children with prenatal and postnatal exposure to high-concentration cannabis products susceptible to adverse physical, neurodevelopmental or cognitive effects from this exposure?

Exclusion Criteria Hierarchy	N =	Citation
No data provided to show association between THC and health effects	4	Sonon et al., 2016[36]; Day et al., 2015[37]; Sonon et al., 2015[38]; Koren et al., 2020[39]
Did not contain population of interest	1	Newcomb et al., 2021[4]
Below THC concentration of interest threshold (<5mg or <10% THC)	1	Gabrhelik et al., 2021[4]
Insufficient data on concentration, frequency, or duration	0	-

REFERENCES FOR APPENDIX TABLES 3-5

1. Ogourtsova T, Kalaba M, Gelinas I, Korner-Bitensky N, Ware MA. Cannabis use and driving-related performance in young recreational users: a within-subject randomized clinical trial. *Canadian Medical Association Open Access Journal*. 2018;6(4):E453-E462.
2. Stevens AK, Aston ER, Gunn RL, et al. Does the combination matter? Examining the influence of alcohol and cannabis product combinations on simultaneous use and consequences in daily life. *Alcoholism: Clinical and Experimental Research*. 2021;45(1):181-193.
3. Braymiller JL, Barrington-Trimis JL, Leventhal AM, et al. Assessment of nicotine and cannabis vaping and respiratory symptoms in young adults. *JAMA network open*. 2020;3(12):e2030189-e2030189.
4. Hoffenberg EJ, McWilliams S, Mikulich-Gilbertson S, Murphy B, Hoffenberg A, Hopfer CJ. Cannabis oil use by adolescents and young adults with inflammatory bowel disease. *Journal of pediatric gastroenterology and nutrition*. 2019;68(3):348-352.
5. Morgan CJ, Freeman TP, Hindocha C, Schafer G, Gardner C, Curran HV. Individual and combined effects of acute delta-9-tetrahydrocannabinol and cannabidiol on psychotomimetic symptoms and memory function. *Translational psychiatry*. 2018;8(1):181.
6. Case KR, Clendennen SL, Tsevat J, Harrell MB. Risk of respiratory, gastrointestinal, and constitutional health symptoms: A cross-sectional study of Texas adolescent and young adult nicotine and marijuana vapers. *Preventive Medicine*. 2022;159:107057.
7. Mackie CJ, Wilson J, Freeman TP, Craft S, De La Torre TE, Lynskey MT. A latent class analysis of cannabis use products in a general population sample of adolescents and their association with paranoia, hallucinations, cognitive disorganisation and grandiosity. *Addictive behaviors*. 2021;117:106837.
8. Stevens AK, Boyle HK, Sokolovsky AW, White HR, Jackson KM. Nuanced relations between simultaneous alcohol and cannabis use motives and negative consequences among college students: The role of multiple product use. *Experimental and Clinical Psychopharmacology*. 2021;
9. Audrain-McGovern J, Stone MD, Barrington-Trimis J, Unger JB, Leventhal AM. Adolescent e-cigarette, hookah, and conventional cigarette use and subsequent marijuana use. *Pediatrics*. 2018;142(3)
10. Gunn RL, Aston ER, Sokolovsky AW, White HR, Jackson KM. Complex cannabis use patterns: Associations with cannabis consequences and cannabis use disorder symptomatology. *Addictive behaviors*. 2020;105:106329.
11. Fares A, Wickens CM, Mann RE, et al. Combined effect of alcohol and cannabis on simulated driving. *Psychopharmacology*. 2021:1-15.
12. Sznitman SR, Vulfsons S, Meiri D, Weinstein G. Medical cannabis and insomnia in older adults with chronic pain: a cross-sectional study. *BMJ supportive & palliative care*. 2020;10(4):415-420.
13. Parks MJ, Maggs JL, Patrick ME. Daily fluctuations in drinking intensity: Links with vaping and combustible use of nicotine and marijuana. *Drug and alcohol dependence*. 2022;233:109347.
14. Tennant FS, Preble M, Prendergast TJ, Ventry P. Medical manifestations associated with hashish. *Jama*. 1971;216(12):1965-1969.
15. Makela P, Wakeley J, Gijsman H, Robson PJ, Bhagwagar Z, Rogers RD. Low doses of Δ-9 tetrahydrocannabinol (THC) have divergent effects on short-term spatial memory in

young, healthy adults. *Neuropsychopharmacology*. 2006;31(2):462-470.
16. Greenberg I, Kuehnle J, Mendelson JH, Bernstein JG. Effects of marihuana use on body weight and caloric intake in humans. *Psychopharmacology*. 1976;49:79-84.
17. Winiger EA, Hitchcock LN, Bryan AD, Bidwell LC. Cannabis use and sleep: expectations, outcomes, and the role of age. *Addictive behaviors*. 2021;112:106642.
18. Ferraro L, Russo M, O'Connor J, et al. Cannabis users have higher premorbid IQ than other patients with first onset psychosis. *Schizophrenia Research*. 2013;150(1):129-135.
19. Roitman P, Mechoulam R, Cooper-Kazaz R, Shalev A. Preliminary, open-label, pilot study of add-on oral Δ 9-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clinical drug investigation*. 2014;34:587-591.
20. Kayser RR, Senter MS, Tobet R, Raskin M, Patel S, Simpson HB. Patterns of cannabis use among individuals with obsessive-compulsive disorder: Results from an internet survey. *Journal of obsessive-compulsive and related disorders*. 2021;30:100664.
21. Matsumoto T, Kawabata T, Okita K, et al. Risk factors for the onset of dependence and chronic psychosis due to cannabis use: Survey of patients with cannabis-related psychiatric disorders. *Neuropsychopharmacology reports*. 2020;40(4):332-341.
22. Smith PA, Slaven M, Shaw E, Chow E, Wolt A. Medical cannabis use in military and police veterans diagnosed with post-traumatic stress disorder (PTSD). *Journal of Pain Management*. 2017;10(4):397-405.
23. Bonn-Miller MO, Brunstetter M, Simonian A, et al. The long-term, prospective, therapeutic impact of cannabis on post-traumatic stress disorder. *Cannabis and cannabinoid research*. 2022;7(2):214-223.
24. Sakal C, Lynskey M, Schlag A, Nutt D. Developing a real-world evidence base for prescribed cannabis in the United Kingdom: preliminary findings from Project Twenty21. *Psychopharmacology*. 2022;239(5):1147-1155.
25. Ferraro L, Murray RM, Di Forti M, et al. IQ differences between patients with first episode psychosis in London and Palermo reflect differences in patterns of cannabis use. *Schizophrenia Research*. 2019;210:81-88.
26. Drost L, DeAngelis C, Lam H, Zaki P, Malek L. Efficacy of different varieties of medical cannabis in relieving symptoms in post-traumatic stress disorder (PTSD) patients. *Journal of Pain Management*. 2017;10(4)(SPECIAL ISSUE: Medical cannabis and clinical practice):415- 422.
27. Martin-Santos R, a Crippa J, Batalla A, et al. Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. *Current pharmaceutical design*. 2012;18(32):4966-4979.
28. Bidwell LC, Ellingson JM, Karoly HC, et al. Association of naturalistic administration of cannabis flower and concentrates with intoxication and impairment. *JAMA psychiatry*. 2020;77(8):787-796.
29. D'souza DC, Ranganathan M, Braley G, et al. Blunted psychotomimetic and amnestic effects of Δ-9-tetrahydrocannabinol in frequent users of cannabis. *Neuropsychopharmacology*. 2008;33(10):2505-2516.
30. Sideli L, Fisher HL, Murray RM, et al. Interaction between cannabis consumption and childhood abuse in psychotic disorders: preliminary findings on the role of different patterns of cannabis use. *Early intervention in Psychiatry*. 2018;12(2):135-142.
31. Schoeler T, Petros N, Di Forti M, et al. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of

psychosis: an observational study. *The Lancet Psychiatry*. 2016/10/01/ 2016;3(10):947-953. doi:https://doi.org/10.1016/ S2215-0366(16)30188-2
32. Bianconi F, Bonomo M, Marconi A, et al. Differences in cannabis-related experiences between patients with a first episode of psychosis and controls. *Psychological Medicine*. 2016;46(5):995-1003.
33. Barrowclough C, Gregg L, Lobban F, Bucci S, Emsley R. The impact of cannabis use on clinical outcomes in recent onset psychosis. *Schizophrenia bulletin*. 2015;41(2):382-390.
34. Martin EL, Strickland JC, Schlienz NJ, et al. Antidepressant and anxiolytic effects of medicinal cannabis use in an observational trial. *Frontiers in Psychiatry*. 2021;12:1554.
35. Kuhathasan N, Minuzzi L, MacKillop J, Frey BN. An investigation of cannabis use for insomnia in depression and anxiety in a naturalistic sample. *BMC psychiatry*. 2022;22(1):1-8.
36. Sonon K, Richardson GA, Cornelius J, Kim KH, Day NL. Developmental pathways from prenatal marijuana exposure to Cannabis Use Disorder in young adulthood. *Neurotoxicology and Teratology*. 2016;58:46-52.
37. Day N, Goldschmidt L, Day R, Larkby C, Richardson G. Prenatal marijuana exposure, age of marijuana initiation, and the development of psychotic symptoms in young adults. *Psychological medicine*. 2015;45(8):1779-1787.
38. Sonon KE, Richardson GA, Cornelius JR, Kim KH, Day NL. Prenatal marijuana exposure predicts marijuana use in young adulthood. *Neurotoxicology and teratology*. 2015;47:10-15.
39. Koren G, Cohen R. The use of cannabis for Hyperemesis Gravidarum (HG). *Journal of Cannabis Research*. 2020;2(1):1-4.
40. Newcomb PA, Ton M, Malen RC, et al. Cannabis use is associated with patient and clinical factors in a population-based sample of colorectal cancer survivors. *Cancer Causes & Control*. 2021;32:1321-1327.
41. Gabrhelík R, Mahic M, Lund IO, et al. Cannabis use during pregnancy and risk of adverse birth outcomes: a longitudinal cohort study. *European addiction research*. 2021;27(2):131-141.

Appendix Table 6: Classification of Study Outcomes for Policy Question 2.

Policy Question 2: Are individuals with preexisting mental health conditions especially susceptible to adverse mental health outcomes of high-concentration cannabis products?

Article	Direction of Association		Cannabis Exposure						
	Dose	Concentration	Product	THC Concentration		Purpose	Route	Frequency	Duration
				Low	High				
GAP Study[1-3]	🟥	🟥	Skunk, Hash / hashish			Recreational	Not reported	Daily	New user, Experienced user
Schoeler 2016[4]	🟥	⬛	Skunk, Hash / hashish			Not reported	Not reported	Monthly, Other	Other
Shelef 2016[5]	🟩	-	Oil	2.5mg	7.5mg	Medicinal	Ingestion	Daily, Other	Other
Cuttler 2018[6]	🟩	🟩	Other	5.5%	26.5%	Medicinal	Inhalation	Not reported	Experienced user
Casarett 2019[7]	🟩	🟩	Cannabis	1%	100%	Not reported	Inhalation	Other	Other
Hergenrather 2020[8]	🟩	-	Cannabis	2000 mg per month	7000 mg per month	Medicinal	Inhalation, Sublingual	Not reported	Experienced user
LaFrance 2020[9]	🟩	⬛	Cannabis	14.42%	16.06%	Other	Inhalation	Other	Not reported
Li 2020[10]	🟩	🟩	Cannabis	10%	35%	Medicinal	Inhalation	Other	Not reported, Other
Madero 2020[11]	🟥	⬛	Cannabis	7mg	490mg	Not reported	Not reported	Weekly, Other	Not reported
Matsumoto 2020[12]	🟩	🟩	Cannabis, Other, Resin			Recreational	Not reported	Daily, Weekly, Monthly	Experienced user

EU-GEI Study 2021[13]	🟥	🟥	Cannabis, Skunk, Hash / hashish, Resin		10%	Not reported	Not reported	Daily, Weekly, Monthly	Experienced user, Other
Stith 2020[14]	🟩	🟩	Cannabis	10%	30%	Medicinal, Recreational	Inhalation	Not reported	Not reported
Bonn-Miller 2021[15]	⬛	⬛	Cannabis	0.03%	12%	Medicinal	Inhalation	Daily	Other
Kayser 2021[16]	⬛	⬛	Cannabis, Concentrate	10%	80%	Medicinal, Recreational	Inhalation, Ingestion	Daily, Monthly	Other
Mauzay 2021[17]	🟩	🟩	Cannabis	0.52%	84%	Not reported	Inhalation	Other	Other

🟩 = Statistically significant beneficial effect
🟥 = Statistically significant adverse effect
⬛ = No statistically significant beneficial or adverse effect
- = No significance test for beneficial or adverse effects

REFERENCES FOR APPENDIX TABLE 6

1. Di Forti M, Sallis H, Allegri F, et al. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia bulletin*. 2014;40(6):1509-1517.
2. Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *The Lancet Psychiatry*. 2015;2(3):233-238.
3. Sideli L, Fisher HL, Murray RM, et al. Interaction between cannabis consumption and childhood abuse in psychotic disorders: preliminary findings on the role of different patterns of cannabis use. *Early intervention in Psychiatry*. 2018;12(2):135-142.
4. Schoeler T, Petros N, Di Forti M, et al. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. *The Lancet Psychiatry*. 2016/10/01/ 2016;3(10):947-953. doi:https://doi.org/10.1016/S2215-0366(16)30188-2
5. Shelef A, Barak Y, Berger U, et al. Safety and efficacy of medical cannabis oil for behavioral and psychological symptoms of dementia: an-open label, add-on, pilot study. *Journal of Alzheimer's disease*. 2016;51(1):15-19.
6. Cuttler C, Spradlin A, McLaughlin RJ. A naturalistic examination of the perceived effects of cannabis on negative affect. *Journal of affective disorders*. 2018;235:198-205.
7. Casarett DJ, Beliveau JN, Arbus MS. Benefit of Tetrahydrocannabinol versus Cannabidiol for Common Palliative Care Symptoms. *J Palliat Med*. Oct 2019;22(10):1180-1184. Comment in: J Palliat Med. 2019 Nov;22(11):1301; PMID: 31661397 [https://www.ncbi.nlm.nih.gov/pubmed/31661397]. doi:https://dx.doi.org/10.1089/jpm.2018.065810.1089/jpm.2018.0658. Epub 2019 Aug 6.
8. Hergenrather JY, Aviram J, Vysotski Y, Campisi-Pinto S, Lewitus GM, Meiri D. Cannabinoid and terpenoid doses are associated with adult ADHD status of medical cannabis patients. *Rambam Maimonides Medical Journal*. 2020;11(1)
9. LaFrance EM, Glodosky NC, Bonn-Miller M, Cuttler C. Short and long-term effects of cannabis on symptoms of post-traumatic stress disorder. *Journal of affective disorders*. 2020;274:298-304.
10. Li X, Diviant JP, Stith SS, et al. Focus: Plant-based Medicine and Pharmacology: The Effectiveness of Cannabis Flower for Immediate Relief from Symptoms of Depression. *The Yale Journal of Biology and Medicine*. 2020;93(2):251.
11. Madero S, Oliveras C, Pons M, et al. Cannabis use the week before admission to psychiatric in-patient service as a marker of severity. *Journal of psychiatric research*. 2020;129:40-46.
12. Matsumoto T, Kawabata T, Okita K, et al. Risk factors for the onset of dependence and chronic psychosis due to cannabis use: Survey of patients with cannabis-related psychiatric disorders. *Neuropsychopharmacology reports*. 2020;40(4):332-341.
13. Sami M, Quattrone D, Ferraro L, et al. Association of extent of cannabis use and psychotic like intoxication experiences in a multi-national sample of first episode psychosis patients and controls. *Psychological medicine*. 2021;51(12):2074-2082.
14. Stith SS, Li X, Diviant JP, et al. The effectiveness of inhaled Cannabis flower for the treatment of agitation/irritability, anxiety, and common stress. *Journal of Cannabis Research*. 2020;2(1):1-14.
15. Bonn-Miller MO, Sisley S, Riggs P, et al. The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial. *PloS one*. 2021;16(3):e0246990.
16. Kayser RR, Senter MS, Tobet R, Raskin M, Patel S, Simpson HB. Patterns of cannabis use among individuals with obsessive-compulsive disorder: Results from an internet survey. *Journal of obsessive- compulsive and related disorders*. 2021;30:100664.
17. Mauzay D, LaFrance EM, Cuttler C. Acute Effects of Cannabis on Symptoms of Obsessive-Compulsive Disorder. *J Affect Disord*. Jan 15 2021;279:158-163. doi:https://dx.doi.org/10.1016/j.jad.2020.09.12410.1016/j.jad.2020.09.124. Epub 2020 Oct 6.

Appendix Table 7: Classification of Study Outcomes for Policy Question 4.

Policy Question Four: Are high-concentration THC cannabis products associated with greater risk of adverse physical or mental health outcomes than lower-concentration products?

Article	Direction of Association		Cannabis Exposure						
	Dose	Concentration	Product	THC Concentration		Purpose	Route	Frequency	Duration
				Low	High				
Cancer Symptom Outcomes									
Levitt 1981[1]	■	■	Unspecified	5 mg	15 mg	Medicinal, Other	Ingestion	Other	Other
Schloss 2021[2]	■	■	Oil	6.9 mg	27 mg	Medicinal	Sublingual	Daily	Chronic
Cardiometabolic Outcomes									
Karniol 1975[3]	-	-	Cannabis	12.5 mg	25 mg	Other	Ingestion	Not reported	Other
Schlienz 2020[4]	-	-	Cannabis	10 mg	50 mg	Other	Ingestion	Weekly, Other	Other
Bidwell 2022[5]	-	-	Cannabis	16%	24%	Other	Inhalation, Ingestion	Other	Other
Gastrointestinal Outcomes									
Schloss 2021[2]	■	■	Oil	6.9 mg	27 mg	Medicinal	Sublingual	Daily	Chronic
Immunity Outcomes									
Peters 2022[6]	-	-	Other	5 mg	20 mg	Other	Ingestion	Daily	Chronic
Driving Performance									
Rafaelsen 1973[7]	■	■	Resin	1%	16.4%	Other	Ingestion	Other	Not reported
Ronen 2008[8]	■	■	Unspecified	13 mg	17 mg	Other	Inhalation	Other	

Lenne 2010[9]	🔴	🔴	Cannabis	7.4 ng/ml	12.0 ng/ml	Other	Inhalation	Other	Other
Hartley 2019[10]	🔴	⚫	Cannabis	10 mg	30 mg	Other	Inhalation	Other	Other
Lopez-Pelayo 2021[11]	🔴	⚫	Cannabis, Hash / hashish, Other	0 mg	21 mg	Not reported	Inhalation, Ingestion, Other	Daily	Other
Marcotte 2022[12]	🔴	⚫	Cannabis	5.9%	13.4%	Other	Inhalation	Other	Other
Mental Health Outcomes									
Noyes 1975[13]	-	-	Unspecified	5 mg	20 mg	Other	Ingestion	Daily	Not reported
Brunt 2014[14]	🔴	🔴	Cannabis	6%	19%	Medicinal	Inhalation, Ingestion	Daily	Other
Hunault 2014[15]	🔴	🔴	Cannabis	29.3 mg	69.46 mg	Other	Inhalation	Other	Other
Wan 2017[16]	-	-	Cannabis	0.1%	28%	Medicinal	Not reported	Not reported, Other	Other
Casarett 2019[17]	🟢	🟢	Cannabis	1%	100%	Not reported	Inhalation	Other	Other
Prince 2019[18]	-	-	Cannabis, Concentrate	20%,	76%	Not reported	Inhalation	Monthly	Other
Stith 2019[19]	🟢	🟢	Cannabis, Concentrate, Other	0%	35%	Medicinal	Inhalation, Topical, Not reported	Not reported	Not reported
Hines 2020[20]	🔴	🔴	Unspecified	<10%	≥10%	Recreational	Inhalation, Not reported	Daily, Weekly, Monthly	Experienced user, Other
Li 2020[21]	🟢	🟢	Cannabis	10%	35%	Medicinal	Inhalation	Other	Not reported, Other
Schlienz 2020[4]	🔴	🔴	Cannabis	10 mg	50 mg	Other	Ingestion	Weekly, Other	Other
Wildes 2020[22]	🔴	🔴	Other	0%	30%	Medicinal, Recreational	Not reported	Daily, Weekly, Monthly	Experienced user

Drennan 2021[23]	🟥🟩	🟥🟩	Concentrate	4.5%	84.99%	Other	Inhalation	Other	Experienced user, Other
Lopez-Pelayo 2021[11]	⬛	⬛	Cannabis, Hash / hashish, Other	0 mg	21 mg	Not reported	Inhalation, Ingestion, Other	Daily	Other
Mauzay 2021[24]	🟩	⬛	Cannabis	0.52%	84%	Not reported	Inhalation	Other	Other
Mueller 2021[25]	🟥	🟥	Cannabis	9%	24%	Recreational	Inhalation	Other	Experienced user
Sainz-Cort 2021[26]	🟥	🟥	Extract	3%	65%	Other	Inhalation	Other	Experienced user, Other
Schloss 2021[2]	⬛	⬛	Oil	6.9 mg	27 mg	Medicinal	Sublingual	Daily	Chronic
Steeger 2021[27]	🟥	⬛	Cannabis, Concentrate	0%, 0 mg	100%, 150 mg	Recreational	Inhalation, Ingestion	Daily, Weekly, Monthly	Experienced user
Peters 2022[6]	-	-	Other	5 mg	20 mg	Other	Ingestion	Daily	Chronic
Neurologic Outcomes									
Ungerleider 1987[28]	🟩	🟩	Unspecified	2.5 mg	15 mg	Other	Ingestion	Daily	New user, Experienced user
Brunt 2014[14]	⬛	⬛	Cannabis	6%	19%	Medicinal	Inhalation, Ingestion	Daily	Other
Hunault 2014[15]	🟥	🟥	Cannabis	29.3 mg	69 mg	Other	Inhalation	Other	Other
Schloss 2021[2]	-	-	Oil	6.9 mg	27 mg	Medicinal	Sublingual	Daily	Chronic
Ocular Outcomes									
Levitt 1981[1]	⬛	⬛	Unspecified	5 mg	15 mg	Medicinal, Other	Ingestion	Other	Other
Pain Outcomes									
Noyes 1975[13]	🟩	🟩	Unspecified	5 mg	20 mg	Other	Ingestion	Other	Not reported
Casarett 2019[17]	🟩	🟩	Cannabis	1%	100%	Not reported	Inhalation	Other	Other

Prince 2019[18]	■	■	Cannabis, Concentrate	20%	76%	Not reported	Inhalation	Monthly	Other
Stith 2019[19]	■	■	Cannabis, Concentrate, Other	0%	35%	Medicinal	Inhalation, Topical, Not reported	Not reported	Not reported
Stith 2020[29]	■	■	Cannabis	0%	35%	Medicinal	Inhalation	Not reported	Acute
Gustavsen 2021[30]	■	■	Oil	2.5 mg	22.5 mg	Medicinal	Sublingual	Daily	Acute
Schloss 2021[2]	■	■	Oil	6.9 mg	27 mg	Medicinal	Sublingual	Daily	Chronic
Psychosocial Outcomes									
Taylor 1976[31]	■	■	Unspecified	0.1 mg/kg	0.3 mg/kg	Other	Ingestion	Other	Experienced user, Other
Weinstein 2008[32]	■	■	Unspecified	13 mg	17 mg	Other	Inhalation	Other	Other
Lopez-Pelayo 2021[11]	■	■	Cannabis, Hash / hashish, Other	0 mg	21 mg	Not reported	Inhalation, Ingestion, Other	Daily	Other
Respiratory Outcomes									
Prince 2019[18]	■	■	Cannabis, Concentrate	20%	76%	Not reported	Inhalation	Monthly	Other
Peters 2022[6]	-	-	Other	5 mg	20 mg	Other	Ingestion	Daily	Chronic
Sexual Health and Reproductive Health Outcomes									
Peters 2022[6]	-	-	Other	5 mg	20 mg	Other	Ingestion	Daily	Chronic
Sleep Outcomes									
Cousens 1973[33]	■	■	Other	10 mg	30 mg	Medicinal	Ingestion	Weekly	Experienced user
Nicholson 2014[34]	■	■	Other	5 mg	15 mg	Other	Other	Other	Experienced user
Sznitman 2020[35]	■	■	Cannabis	*	15.6%	Medicinal	Not reported	Weekly	Other

Gustavsen 2021[30]	-	-	Oil	2.5 mg	22.5 mg	Medicinal	Sublingual	Daily	Acute
Lopez-Pelayo 2021[11]	■	■	Cannabis, Hash / hashish, Other	0 mg	21 mg	Not reported	Inhalation, Ingestion, Other	Daily	Other
Schloss 2021[2]	■	■	Oil	6.9 mg	27 mg	Medicinal	Sublingual	Daily	Chronic
Winiger 2021[36]	■	■	Cannabis, Concentrate	0%	30%	Not reported	Inhalation, Ingestion	Daily, Weekly, Monthly	Experienced user
Peters 2022[6]	-	-	Other	5 mg	20 mg	Other, Experimental	Ingestion	Daily	Chronic
Substance Use / Substance Dependence Outcomes									
Prince 2019[18]	■	■	Cannabis, Concentrate	20%	76%	Not reported	Inhalation	Monthly	Other
Hines 2020[20]	■	■	Unspecified	<10%	≥10%	Recreational	Inhalation, Not reported	Daily, Weekly, Monthly	Experienced user, Other
Lopez-Pelayo 2021[11]	■	■	Cannabis, Hash / hashish, Other	0 mg	21 mg	Not reported	Inhalation, Ingestion, Other	Daily	Other
Steeger 2021[27]	■	■	Cannabis, Concentrate	0%, 0 mg	100%, 150 mg	Recreational	Inhalation, Ingestion	Daily, Weekly, Monthly	Experienced user
Other Outcome Domains									
Dry Mouth									
Cousens 1973[33]	-	-	Other	10 mg	30 mg	Medicinal	Ingestion	Weekly	Experienced user
Hunault 2014[15]	■	■	Cannabis	29.3 mg	69 mg	Other	Inhalation	Other	Other
Peters 2022[6]	-	-	Other	5 mg	20 mg	Other	Ingestion	Daily	Chronic
Gustavsen 2021[30]	-	-	Oil	2.5 mg	22.5 mg	Medicinal	Sublingual	Daily	Acute
Overall Perceived Health									
Stith 2019[19]	■	■	Cannabis, Concentrate, Other	0%	72 35%	Medicinal	Inhalation, Topical, Not reported	Not reported	Not reported

Steeger 2021[27]	■	■	Cannabis, Concentrate	0%, 0 mg	100%, 150 mg	Recreational	Inhalation, Ingestion	Daily, Weekly, Monthly	Experienced user
Prince 2019[18]	■	■	Cannabis, Concentrate	20%	76%	Not reported	Inhalation	Monthly	Other

*Average THC reported, THC correlated with outcome.

■ = Statistically significant beneficial effect

■ = Statistically significant adverse effect

■ = No statistically significant beneficial or adverse effect

- = No significance test for beneficial or adverse effects

REFERENCES FOR APPENDIX TABLE 7

1. Levitt M, Wilson A, Bowman D, et al. Physiologic observations in a controlled clinical trial of the antiemetic effectiveness of 5, 10, and 15 mg of delta 9-tetrahydrocannabinol in cancer chemotherapy. Ophthalmologic implications. *Journal of clinical pharmacology*. 1981;21(S1):103S-109S.
2. Schloss J, Lacey J, Sinclair J, et al. A Phase 2 Randomised Clinical Trial Assessing the Tolerability of Two Different Ratios of Medicinal Cannabis in Patients With High Grade Gliomas. *Front Oncol*. 2021;11:649555. doi:https://dx.doi.org/10.3389/fonc.2021.64955510.3389/fonc.2021.649555. eCollection 2021.
3. Karniol IG, Shirakawa I, Takahashi RN, Knobel E, Musty RE. Effects of delta9-tetrahydrocannabinol and cannabinol in man. *Pharmacology*. 1975;13(6):502-12. doi:https://dx.doi.org/10.1159/00013694410.1159/000136944.
4. Schlienz NJ, Spindle TR, Cone EJ, et al. Pharmacodynamic dose effects of oral cannabis ingestion in healthy adults who infrequently use cannabis. *Drug Alcohol Depend*. Mar 21 2020;211:107969. doi:https://dx.doi.org/10.1016/j.drugalcdep.2020.10796910.1016/j.drugalcdep.2020.107969.
5. Bidwell LC, Karoly HC, Torres MO, Master A, Bryan AD, Hutchison KE. A naturalistic study of orally administered vs. inhaled legal market cannabis: cannabinoids exposure, intoxication, and impairment. *Psychopharmacology (Berl)*. Feb 2022;239(2):385-397. doi:10.1007/s00213-021-06007-2
6. Peters EN, Mosesova I, MacNair L, et al. Safety, Pharmacokinetics and Pharmacodynamics of Spectrum Red Softgels in Healthy Participants. Randomized Controlled Trial. *Journal of Analytical Toxicology*. 2022;46(5):528-539.
7. Rafaelsen OJ, Bech P, Christiansen J, Christrup H, Nyboe J, Rafaelsen L. Cannabis and alcohol: effects on stimulated car driving. *Science*. Mar 2 1973;179(4076):920-3. doi:https://dx.doi.org/10.1126/science.179.4076.92010.1126/science.179.4076.920.
8. Ronen A, Gershon P, Drobiner H, et al. Effects of THC on driving performance, physiological state and subjective feelings relative to alcohol. *Accid Anal Prev*. May 2008;40(3):926-34. doi:https://dx.doi.org/10.1016/j.aap.2007.10.01110.1016/j.aap.2007.10.011. Epub 2007 Nov 26.
9. Lenne MG, Dietze PM, Triggs TJ, Walmsley S, Murphy B, Redman JR. The effects of cannabis and alcohol on simulated arterial driving: Influences of driving experience and task demand. *Accid Anal Prev*. May 2010;42(3):859-66. doi:https://dx.doi.org/10.1016/j.aap.2009.04.02110.1016/j.aap.2009.04.021.
10. Hartley S, Simon N, Larabi A, et al. Effect of Smoked Cannabis on Vigilance and Accident Risk Using Simulated Driving in Occasional and Chronic Users and the Pharmacokinetic-Pharmacodynamic Relationship. *Clin Chem*. May 2019;65(5):684-693. doi:https://dx.doi.org/10.1373/clinchem.2018.29972710.1373/clinchem.2018.299727. Epub 2019 Mar 14.
11. Lopez-Pelayo H, Campeny E, Oliveras C, et al. Early, Chronic, and Acute Cannabis Exposure and Their Relationship With Cognitive and Behavioral Harms. *Front Psychiatry*. 2021;12:643556. doi:https://dx.doi.org/10.3389/fpsyt.2021.64355610.3389/fpsyt.2021.643556. eCollection 2021.
12. Marcotte TD, Umlauf A, Grelotti DJ, et al. Driving Performance and Cannabis Users' Perception of Safety: A Randomized Clinical Trial. *JAMA Psychiatry*. Mar 1 2022;79(3):201-209. doi:10.1001/jamapsychiatry.2021.4037
13. Noyes R, Jr B, S. F B, D. A C. Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol*. Feb-Mar 1975;15(2-3):139-43. doi:https://dx.doi.org/10.1002/j.1552-4604.1975.tb02348.x10.1002/j.1552-4604.1975.tb02348.x.

14. Brunt TM, van Genugten M, Honer-Snoeken K, van de Velde MJ, Niesink RJ. Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. *J Clin Psychopharmacol*. Jun 2014;34(3):344-9. doi:https://dx.doi.org/10.1097/JCP.000000000000012910.1097/JCP.0000000000000129.

15. Hunault CC, Bocker KB, Stellato RK, Kenemans JL, e Vries I, Meulenbelt J. Acute subjective effects after smoking joints containing up to 69 mg Delta9-tetrahydrocannabinol in recreational users: a randomized, crossover clinical trial. *Psychopharmacology (Berl)*. Dec 2014;231(24):4723-33. doi:https://dx.doi.org/10.1007/s00213-014-3630-210.1007/s00213-014-3630-2. Epub 2014 May 31.

16. Wan BA, Diaz P, Blake A, et al. Efficacy of different varieties of medical cannabis in relieving symptoms. Article. *Journal of Pain Management*. 2017;10(4):375-383.
17. Casarett DJ, Beliveau JN, Arbus MS. Benefit of Tetrahydrocannabinol versus Cannabidiol for Common Palliative Care Symptoms. *J Palliat Med*. Oct 2019;22(10):1180-1184. Comment in: J Palliat Med. 2019 Nov;22(11):1301; PMID: 31661397 [https://www.ncbi.nlm.nih.gov/pubmed/31661397]. doi:https://dx.doi.org/10.1089/jpm.2018.065810.1089/jpm.2018.0658. Epub 2019 Aug 6.

18. Prince MA, Conner BT. Examining links between cannabis potency and mental and physical health outcomes. *Behaviour Research and Therapy*. 2019;115:111-120.
19. Stith SS, Vigil JM, Brockelman F, Keeling K, Hall B. The Association between Cannabis Product Characteristics and Symptom Relief. *Sci Rep*. Feb 25 2019;9(1):2712. doi:https://dx.doi.org/10.1038/s41598-019-39462-110.1038/s41598-019-39462-1.

20. Hines LA, Freeman TP, Gage SH, et al. Association of High-Potency Cannabis Use With Mental Health and Substance Use in Adolescence. *JAMA Psychiatry*. Oct 1 2020;77(10):1044-1051. doi:https://dx.doi.org/10.1001/jamapsychiatry.2020.103510.1001/jamapsychiatry.2020.1035.

21. Li X, Diviant JP, Stith SS, et al. Focus: Plant-based Medicine and Pharmacology: The Effectiveness of Cannabis Flower for Immediate Relief from Symptoms of Depression. *The Yale Journal of Biology and Medicine*. 2020;93(2):251.
22. Wildes M, Bigand TL, Layton ME, Wilson M. Cannabis Use and Cognition in Adults Prescribed Opioids for Persistent Pain. *Pain Manag Nurs*. Feb 2020;21(1):94-99. doi:https://dx.doi.org/10.1016/j.pmn.2019.06.01410.1016/j.pmn.2019.06.014. Epub 2019 Aug 9.

23. Drennan M, Karoly H, Bryan A, Hutchison K, Bidwell L. Acute objective and subjective intoxication effects of legal-market high potency THC-dominant versus CBD-dominant cannabis concentrates. *Scientific reports*. 2021;11(1):21744.
24. Mauzay D, LaFrance EM, Cuttler C. Acute Effects of Cannabis on Symptoms of Obsessive-Compulsive Disorder. *J Affect Disord*. Jan 15 2021;279:158-163. doi:https://dx.doi.org/10.1016/j.jad.2020.09.12410.1016/j.jad.2020.09.124. Epub 2020 Oct 6.

25. Mueller RL, Ellingson JM, Bidwell LC, Bryan AD, Hutchison KE. Are the Acute Effects of THC Different in Aging Adults? *Brain Sci*. May 1 2021;11(5)doi:https://dx.doi.org/10.3390/brainsci1105059010.3390/brainsci11050590.

26. Sainz-Cort A, Jimenez-Garrido D, Munoz-Marron E, Viejo-Sobera R, Heeroma J, Bouso JC. Opposite Roles for Cannabidiol and delta-9-Tetrahydrocannabinol in Psychotomimetic Effects of Cannabis Extracts: A Naturalistic Controlled Study. *J Clin Psychopharmacol*. Sep-Oct 01 2021;41(5):561-570. doi:https://dx.doi.org/10.1097/JCP.000000000000145710.1097/JCP.0000000000001457.

27. Steeger CM, Hitchcock LN, Bryan AD, Hutchison KE, Hill KG, Bidwell LC. Associations between self-reported cannabis use frequency, potency, and cannabis/health metrics. *Int J Drug Policy*. Nov 2021;97:103278. doi:https://dx.doi.org/10.1016/j.drugpo.2021.10327810.1016/j.drugpo.2021.103278. Epub 2021 May 30.

28. Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW. Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. *Adv Alcohol Subst Abuse*. 1987;7(1):39-50. doi:https://dx.doi.org/10.1300/j251v07n01_0410.1300/j251v07n01_04.

29. Stith SS, Diviant JP, Brockelman F, et al. Alleviative effects of Cannabis flower on migraine and headache. *J Integr Med*. Sep 2020;18(5):416-424. doi:https://dx.doi.org/10.1016/j.joim.2020.07.00410.1016/j.joim.2020.07.004. Epub 2020 Jul 18.

30. Gustavsen S, Hb S, K L, et al. Safety and efficacy of low-dose medical cannabis oils in multiple sclerosis. *Mult Scler Relat Disord*. Feb 2021;48:102708. doi:https://dx.doi.org/10.1016/j.msard.2020.10270810.1016/j.msard.2020.102708. Epub 2020 Dec 30.

31. Taylor SP, Vardaris RM, Rawtich AB. The effects of alcohol and delta 9 tetrahydrocannabinol on human physical aggression. *Aggressive Behavior*. 1976;2(2):153-161.
32. Weinstein A, Brickner O, Lerman H, et al. A study investigating the acute dose-response effects of 13 mg and 17 mg Delta 9- tetrahydrocannabinol on cognitive-motor skills, subjective and autonomic measures in regular users of marijuana. *J Psychopharmacol*. Jun 2008;22(4):441-51. doi:https://dx.doi.org/10.1177/026988110808819410.1177/0269881108088194.

33. Cousens K, DiMascio A. (-) Delta 9 THC as an hypnotic. An experimental study of three dose levels. *Psychopharmacologia*. 1973;33(4):355-64.
34. Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of Delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol*. Jun 2004;24(3):305-13. doi:https://dx.doi.org/10.1097/01.jcp.0000125688.05091.8f10.1097/01.jcp.0000125688.05091.8f.

35. Sznitman SR, Vulfsons S, Meiri D, Weinstein G. Medical cannabis and insomnia in older adults with chronic pain: a cross-sectional study. *BMJ supportive & palliative care*. 2020;10(4):415-420.
36. Winiger EA, Hitchcock LN, Bryan AD, Bidwell LC. Cannabis use and sleep: expectations, outcomes, and the role of age. *Addictive behaviors*. 2021;112:106642.