Official Title: Interaction Between Cannabidiol, Meal Ingestion, and Liver Function

Identifiers: NCT04971837 Unique Protocol ID: 21-10634H

Study Documents:

- IRB Approved Study Protocol: Last approval Date 03/24/2021. Separate Study Protocol does not exist only the IRB application format
- Informed Consent: Last approval Date 03/24/2021
- Statistical Analysis Plan: Manuscript with statistical analysis plan submitted 04/01/2022

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* * * Personnel Information * * *

Principal Investigator Mandatory

CSU defines "Investigator" as an individual who conducts a research study. If the study is conducted by a team of individuals, the Investigator is the responsible leader of the team. Students, fellows and residents may not act as a Principal Investigator.

Name of Principal Investigator*		Degree (MD/PhD/BSN/etc.)		Title
Bell, Christopher				Associate Professor
Email*		**Phone**		**Fax**
Christopher.Bell@ColoState.EDU		(970) 491-7522		
Research Department		**CSU Status Check ALL that apply***		**Mailing Address**
Health and Exercise Science	X	Faculty		
		Staff		
		Other		

ALL research personnel are required to complete Human Subject Research training from CITI within the last 3 years prior to engaging in any research-related activities. Go to CITI Program to complete.

Any NIH funded clinical trials require GCP training.

The Research Compliance Office will verify the last date of completion below.

CITI Training Date*	Type of CITI training completed.*
08/06/2020	Group 1 Biomedical

Training Details

No training data is available.

CO-Principal Investigator

Name of Co-Principal Investigator*		Degree (MD/PhD/BSN/etc.)		Title
Email*		**Phone**		**Fax**
Research Department		**CSU Status Check ALL that apply***		**Mailing Address**
		Faculty		
		Staff		
		Other		

ALL research personnel are required to complete Human Subject Research training from CITI within the last 3 years prior to engaging in any research-related activities. Go to CITI Program to complete.

Any NIH funded clinical trials require GCP training.

The Research Compliance Office will verify the last date of completion below.

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CITI Training Date	Type of CITI training completed.*
Training Details	
No training data is available.	

Department Head Mandatory

Name of Department Head*		Degree (MD/PhD/BSN/etc.)		Title
Braun, Barry				Professor
Email*		**Phone**		**Fax**
Barry.Braun@colostate.edu				
Research Department		**CSU Status Check ALL that apply***		**Mailing Address**
Health and Exercise Science	X	Faculty		
		Staff		
		Other		

Department Head is not required to have completed Human Subjects Training, but this section will require entry under Type of CITI Training completed. Please select one from the drop down menu.

CITI Training Date	Type of CITI training completed.*
	Group 1 Biomedical
Training Details	
No training data is available.	

Administrative Contact--This is not a required position.

Name of Administrative Contact*		Degree (MD/PhD/BSN/etc.)		Title
Email*		**Phone**		**Fax**
Research Department		**CSU Status Check ALL that apply***		**Mailing Address**
		Faculty		
		Staff		
		Other		

Administrative Contact is not required to have completed Human Subjects Training unless they are engaged in research activities, but this section will require entry under Type of CITI Training completed. Please select one from the drop down menu.

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CITI Training Date	Type of CITI training completed.*
Training Details	
No training data is available.	

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* * * Subject Checklist * * *

Subject Checklist

Select All That Apply :

- Children under 18
- Pregnant women
- Fetuses/neonates
- Prisoners
- Military personnel
- X Adult Volunteers
- Economically/educationally disadvantaged
- Individuals with impaired decision-making capacity
- X University students
- X University employees
- Illiterate
- Homeless
- Public officials/candidates for public office
- Institutionalized patients/residents
- Persons incompetent to give consent (e.g., dementia, comatose, have legal guardians)
- X Healthy Individuals
- Existing Data - No prospective participants will be involved.

Other (please specify):

---

* * * Study Location * * *

Study Location

Select All That Apply - NOTE: Check "Other" and input text: 1.) If your study location is not listed, or 2.) If you would like to list details of your already-checked location (e.g., specific school within a school district)

- X Colorado State University
- Colorado State University - Pueblo
- University of Colorado Health

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University of Colorado Boulder
University of Colorado - Colorado Springs
University of Colorado Denver
Other University/College
Other Medical/Health Care Facility
School/School District
Other (please specify)

Has this protocol been submitted to any other Institutional Review Board not listed above?	N
Is this a cooperative research project (projects involving more than one institution)? Federally funded cooperative research projects are required to rely on a single IRB, which will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution.	N
Is this a multi-site clinical trial (a study where different PIs at different institutions are conducting the same study or aspects of the same study)?	N
If yes to multi site clinical trial or cooperative research project, will Colorado State University function as the coordinating center or lead institution?	N

Please submit your grant proposal and any site documentation for any site not under the jurisdiction of the CSU IRBs in the Attachment section.

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* * * General Checklist * * *

General Checklist

Select All That Apply :

Request to Rely on Another IRB - Please upload completed Request to Rely and associated documents in attachment section

IRB Authorization Agreement (IAA), Memorandum Of Understanding (MOU), etc. attach documentation in the Attachments section (This only applies to studies where the CSU IRB is the Reviewing IRB).

FDA regulated Clinical Trial (must be registered on ClinicalTrials.gov, see below)

NIH funded Clinical Trial study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical OR behavioral health-related outcomes. Additional requirements including ClinicalTrials.gov registration, Certificate of Confidentiality, etc. that impact your consent forms and procedures.

HHS defined Clinical Trial: Federally funded study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical OR behavioral health-related outcomes. Be aware of additional requirements in posting consent forms https://www.hhs.gov/ohrp/regulations-and-policy/informed-consent-posting/index.html)

Existing Data Sets

Interview

X Questionnaire/Survey

Graduate Level Thesis/Dissertation Project (Please upload methodology section of your proposal in Attachments section.) Please coordinate your procedures with Data Management Services in CSU Libraries: https://lib.colostate.edu/services/electronic-theses-and-dissertations-etds/

Data Management Plan/Data Safety Monitoring Board Plan: Please coordinate your procedures with Data Management Services in CSU Libraries: https://lib.colostate.edu/services/electronic-theses-and-dissertations-etds/

Radioisotopes/radiation-producing machines, even if standard of care (contact Radiation Safety James.Abraham@colostate.edu)

X Human blood, cells, tissues, or body fluids (Institutional BioSafety Approvals at RICRO_IBC@colostate.edu)

Tissues to be stored for future research projects

Data/Tissues to be sent out of this institution as part of a research agreement (Data Use Agreement or Material TransferAgreement

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(MTA)

Human Embryos

Human Embryonic Cells -- Provide NIH Code Number(s) or state that no federal funding will be used to support this research.

Use of Patient related equipment? If Yes, specify what equipment is being used.

Medical equipment used for human patients/subjects also used on animals.

Protocol involves studying Cannabis/Hemp/CBD. Learn the current status of Cannabis & Hemp Research at CSU: https://www.research.colostate.edu/ricro/cannabis-research/

Protocol involves studying potentially addicting drugs.

Investigational drugs, reagents, or chemicals

Commercially available drugs, reagents, or other chemicals administered to subjects (even if they are not being studied)

Investigational Device

This study involves drugs or devices regulated by FDA

Cancer Subjects (e.g., clinical trials, behavior/prevention) or Cancer Tissues (e.g., blood, cells, body fluids).

X This study is or will be posted on ClinicalTrials.gov (https://www.research.colostate.edu/ricro/qa/clinicaltrials-gov/request-an-account/). Registration on clinicaltrials.gov must be done within 21 days of your first participant enrollment (signing of consent).

If checked, please provide NCT number here. If not registered yet, please update when completed: Not Yet Registered

Protected Health Information (PHI) will be viewed, created, accessed, used, or disclosed.

HIPAA Authorization

Waiver or Alteration of Authorization

Activities Preparatory to Research

Limited Data Set and Data Use Agreement

Use and Disclosure of Decedents PHI without Authorization

Class Project: If the intention of your project is specific to only meeting a course requirement and not intended to be disseminated outside the class, please complete the Human Subjects Determination form for guidance, if you need further guidance.

Other (clarify in text box to the right)

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* * * Funding * * *

NONE--This project does not have any funding. If you want to add Funding for the study, please uncheck "NONE."

Funding

Add external and internal grant funding source(s) below: Federal Government, Other Gov. (i.e., State, local), Foundation or Other. Select "None" above if there is no external funding for the study.

It is CSU Policy to review grant applications with IRB submissions for congruency. Upload your grant in the attachment section.

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Industry/Privately Sponsored/Funded

Funding Sponsor/Company:	Contact Name:
Caliper Foods	Keith Woeflel

Industry/Privately Sponsored/Funded

Funding Sponsor/Company: Caliper Foods
If study is not occurring at CSU, you must provide the following:
Address: 6360 E. 58th
City: Commerce City
State: CO
Zip: 80022-3969
Phone:
Fax:
Contact Name: Keith Woeflel
Amount Due Invoice:

X Funding for this study was secured by the Office of Sponsored Programs. As principal investigator, I will provide my IRB approval documentation with OSP upon receipt.

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* * * Application Type Checklist * * *

Application type checklist

Not Human Subjects Research
Exempt
X Expedited/Full Board

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* * * Expedited Paragraphs * * *

PLEASE READ: For Expedited Review, all aspects of the research must include activities that (1) present no more than minimal risk to human subjects, and (2) involve one or more of the specific categories listed below. If any research activity is outside the expedited categories, the review must be conducted by a fully convened IRB.

Select the following applicable categories to determine if your research project qualifies under Expedited Review. If none of the categories are applicable to your research project, a Full Committee Review will be required. For Expedited or Full Review, proceed to complete the following application.If none of the expedited criteria are appropriate for your project, please move to the next screen WITHOUT checking any of these criteria; your protocol will be reviewed by the full IRB. Note: The IRB will make the final determination if your protocol is eligible for expedited review.

Select one or more of the following paragraph(s):

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1. **Clinical studies of drugs and medical devices only when condition (a) and (b) are met.**

   a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

   b) Research on medical devices for which

      i) An investigational device exemption application (21 CFR Part 812) is not required; or

      ii) The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. **Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:**

   a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

   b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. **Prospective collection of biological specimens for research purposes by non-invasive means.**

   Examples:

   a) Hair and nail clippings in a non-disfiguring manner;

   b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction;

   c) Permanent teeth if routine patient care indicates a need for extraction;

   d) Excreta and external secretions (including sweat);

   e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue;

   f) Placenta removed at delivery;

   g) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor;

   h) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques;

   i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings;

   j) Sputum collected after saline mist nebulization.

4. **Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)**

   Examples:

   a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;

   b) Weighing or testing sensory acuity;

   c) Magnetic resonance imaging;

   d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;

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e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. **Research involving materials (data, documents, records, or specimen) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). (NOTE: Some research in this paragraph may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)**

6. **Collection of data from voice, video, digital, or image recordings made for research purposes.**

7. **Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects - 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)**

* * * Summary, Purpose, Procedures * * *

Title (Please indicate if the protocol title is different from the proposal title)

Interaction between Cannabidiol, Meal Ingestion, and Liver Function

Proposed Start Date: 04/16/2021 **Proposed End Date:** 04/15/2022

1. Summary

a) **Provide a brief summary of the scope of work of this project, using non-technical terms that would be understood by a non-scientific reader. This summary should be no more than 200 words.Did you know that your consent is a great tool to reference the information for this section?**

According to a recent consumer poll, over 20 million Americans regularly use cannabidiol (CBD). Moreover, 64 million Americans (over 25% of the population) report trying CBD at least once within the previous 2 years. Since the passing of the 2018 Agriculture Improvement Act, the use of hemp-derived products, such as CBD, is highly prevalent across North America. The acceleration of the use of CBD has outpaced our understanding of the associated potential risks and benefits, and the way it is processed within the body.

In the current proposed project, we wish to continue our ongoing collaboration with Caliper Foods, a Colorado-based manufacturer of CBD products. The focus of this project is three-fold: (1) we will compare the pharmacokinetics of different formulations of ingestible CBD; (2) we will examine the potential two-way interaction between a meal and one formulation of ingestible CBD; and, (3) we will examine the influence of different formulations of CBD on markers of liver function.

PLEASE NOTE: This study is currently unfunded but we have a verbal agreement in place and a contract is in formal development/review. We will update the IRB as the funding status officially changes and submit a formal copy of the contracted research proposal

2. Purpose

a) **Describe the purpose for the proposed project as well as the hypotheses/research questions to be examined. What are your primary, secondary, and tertiary objectives?**

Pharmacokinetics describes the speed in which something that is ingested is made available within the body (i.e. bioavailability). There are many different preparations/formulations of CBD and they may differ from one another with regards to their pharmacokinetics. One important consideration when evaluating CBD formulations is the pharmacokinetic goal and intended use. For example, if the indication for the CBD is to treat acute pain, then a faster time to peak concentration (Tmax) and higher maximal concentration (Cmax) may be desirable, and also may help to decrease the risk of overdose due to premature repeat self-administration. Alternatively, as a chronic treatment for anxiety, a larger area under the curve (AUC) may be preferable if a user follows a regular dosing schedule.

One purpose of the proposed project is to compare the pharmacokinetics of different formulations of CBD. The formulations will be standardized for CBD dose (30 mg) but will differ in their preparation (e.g. water vs. fat-soluble).

Several previous studies have demonstrated an influence of eating on the pharmacokinetics of ingested CBD. The general

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consensus appears to be that prior ingestion of a high-fat meal increases the maximal concentration of circulating CBD (Cmax) and lowers the time to attain peak circulating concentration (Tmax).

One purpose of the proposed project is to study the influence of a standardized meal on the pharmacokinetics of a CBD formulation.

Little is known about the influence of ingested CBD on postprandial metabolism. The thermic effect of feeding (i.e. the increase in metabolic rate above resting metabolism) is considered an important physiological determinant of energy balance, and therefore also of weight gain or loss. Further, the dynamics of circulating glucose and triglycerides following a meal are reflective of metabolic health and predictive of future cardiometabolic disease risk. CBD has been purported to have a variety of beneficial physiological properties, including anti-inflammatory and antioxidant actions. Either of these individual properties alone could favorably modify postprandial metabolism, given that CBD potentially does both, it appears likely that CBD might improve the physiological regulation of postprandial metabolism.

One purpose of the proposed project is to determine the influence of CBD on postprandial metabolism.

The liver plays a critical regulatory role in postprandial metabolism, and also with the physiological processing of cannabinoids. The relationship between the use of cannabinoids and liver health is unclear. While early studies implied that exposure of the liver to very high daily dosing of cannabinoids may be detrimental, more recent studies are suggesting that some cannabinoids, including CBD, may have therapeutic potential for the treatment of non-alcoholic fatty liver disease. The acute effects of low dose CBD (e.g. 30 mg) on liver function in healthy adults have not been well described, and may be influenced by the formulation of the CBD product (i.e. whether it is water or lipid soluble).

One purpose of the proposed project is to determine the acute influence of different formulations of CBD on circulating markers of liver function.

b) What do the investigators hope to learn from this project?

We hope to learn a little more about how the formulation of CBD influences the speed in which it is processed within the body, how CBD and a meal may interact (i.e. how does CBD influence the digestion of a meal, and how does a meal influence the processing of CBD), and if low-dose CBD (30 mg) influences liver function.

c) Please describe your plans to share the results of this study with intentions to influence behavior, practice, theory, future research designs.

The results of the study will be submitted for publication in peer-reviewed scientific journals, and presented at scientific conferences. In light of the prevalence of CBD use in the USA, we hope the study will provide users and manufacturers with useful physiological information about CBD. Noteworthy, our previous CBD study (IRB Protocol 19-9577H) was published on January 6th, 2021. Since publication, the abstract has been viewed 1,307 times, and the full manuscript accessed 970 times (articles metrics as of March 2, 2021).

3. Procedures

a) Describe in chronological order of event(s) how the activities will be conducted, providing information about all procedures (e.g. interventions/interactions with subjects, data collection, photographing, audio and video recording), including follow up procedures. Please provide details of all research activities that a participant will be involved.

OVERVIEW
Adult men and women will be invited to participate. Inclusion criteria will include: age over 18 years, body mass greater than 110 Lbs (50 kg), body mass index greater than 25 kg/m^2, absence of any gastrointestinal or metabolic diseases, and ability to refrain from use of any Cannabis or cannabis containing products for three days prior to each laboratory visit. The goal is to complete all experimental procedures in 15 adults.

Following screening (i.e. medical history, and assessment of body composition via dual energy X-ray absorptiometry (DEXA)) participants will report to the lab on seven separate occasions separated by a minimum of 4-days. Participants will arrive in the morning having abstained from food for 12-hours, and any products containing CBD for 72-hours. On arrival participants will be instrumented for measurement of heart rate and blood pressure. A venous catheter will be introduced to an arm or hand vein and kept patent via a
saline drip.

Two of the visits will begin with measurement of resting metabolic rate followed immediately by ingestion of a liquid meal and a single 30 mg dose of CBD or a placebo. Postprandial metabolism will be studied using indirect calorimetry and repeated blood sampling for circulating markers of carbohydrate and fat metabolism. Blood will also be sampled for determination of CBD pharmacokinetics and analysis of blood for circulating markers of liver function.

The other five visits will comprise ingestion of different CBD formulations without a meal. Venous blood will be sampled at

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standardized intervals over 4-hours and will be analyzed for circulating CBD concentration and markers of liver function.

DETAILS
Visit 1: Screening Visit - Duration: ~ 0.5 hour
During this visit participants will complete the Informed Consent, provide a brief medical history, and will undergo basic measures of body composition (height, weight, and waist and hip circumference, and DEXA). Body composition is a known physiological regulator of CBD concentration, and is related to metabolic rate and postprandial metabolism. DEXA data will be used as a statistical co-variable in our final analysis.

The remaining seven visits will occur in a random order. Five of these visits will be almost identical, differing only in the preparation, but not the dose, of CBD. The other two visits will be almost identical to the other five but they will also include measurement of resting metabolism, ingestion of a meal, measurement of metabolic rate following the meal, and one of the visits will entail the substitution of a placebo for CBD.

Five Visits Not Involving A Test Meal ~ 4.5 hours each
Participants will report to the lab on five separate occasions separated by a minimum of 5-days. Participants will arrive in the morning having abstained from food for 12-hours, and any products containing CBD for 72-hours. On arrival participants will be instrumented for measurement of heart rate and blood pressure. A venous catheter will be introduced to an arm or hand vein and kept patent via a saline drip.

Following baseline blood sampling (time 0), participants will ingest one of the product formulations. Venous blood will be sampled at standardized intervals over 4-hours: 0, 10, 20, 30, 45, 60, 120, 180, and 240 minutes and will be analyzed for circulating CBD concentration. Each blood sample will be ~5 mL.

In addition, venous blood will also be sampled and analyzed for circulating factors indicative of liver (and also kidney) function, including alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase, total bilirubin, and blood urea nitrogen. These samples will be taken at time 0, 60 and 240 minutes. Each of these blood samples will be ~1 mL.

The following formulations will be studied. All products will be standardized to 30mg CBD per dose.

1)T-P-S-10 Caliper powder - 30 mg CBD in the form of 300 mg of 10% CBD isolate
2)Oil based tincture - 30 mg CBD isolate in MCT oil (1:1 ratio of CBD to MCT oil)
3)10% CBD Gum Arabic, maltodextrin base
4)10% CBD Gum Arabic, sorbitol base
5)CBD Isolate in water

One of the non test meal visits, the visit in which T-P-S-10 Caliper powder - 30 mg CBD in the form of 300 mg of 10% CBD isolate is ingested will also involve additional blood sampling for the measurement of glucose, insulin and triglyceride concentration at time -5, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes. Each of these blood samples will be ~3 mL.

Two Visits Involving a Test Meal ~ 5.5 hours each
Participants will report to the lab on two separate occasions separated by a minimum of 5-days. Participants will arrive in the morning having abstained from food for 12-hours, and any products containing CBD for 72-hours. On arrival participants will be instrumented for measurement of heart rate and blood pressure. A venous catheter will be introduced to an arm or hand vein and kept patent via a saline drip.

Resting Metabolic Rate (ventilated hood technique,indirect calorimetry) for 45 minutes and blood pressure and heart rate will be measured.

Participants will ingest a meal. The meal will consist of a commercially available liquid mixed meal (Boost Balanced Nutrition Drink; Nestle Health and Science, 15% DV carbohydrate, 5% DV fat, 20% DV protein). The total number of calories will be the equivalent of 40% of RMR, resulting in a meal approximately equivalent to 30% of total daily caloric requirements. The meal will be ingested within 10-minutes. Immediately after the meal, participants will ingest a placebo or CBD (T-P-S-10 Caliper powder - 30 mg CBD in the form of 300 mg of 10% CBD isolate).

Immediately after the meal and CBD ingestion, measurement of metabolic rate (ventilated hood technique, indirect calorimetry) will begin. Measurements lasting 25 minutes will be performed at 0, 30, 60, 90, 120, 150, 180, and 210 minutes. At the end of each 25-minute measurement, the ventilated hood will be removed to provide the participant with a 5-minute break.

Venous blood will be sampled at standardized intervals over 4-hours: 0, 10, 20, 30, 45, 60, 120, 180, and 240 minutes and will be analyzed for circulating CBD concentration. Each blood sample will be ~5 mL.

In addition, venous blood will also be sampled and analyzed for circulating factors indicative of liver (and also kidney) function, including alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase, total bilirubin, and blood urea

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nitrogen. These samples will be taken at time 0, 60 and 240 minutes. Each of these blood samples will be ~1 mL.

Blood sampling for the measurement of glucose, insulin and triglyceride concentration at time -5, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes. Each of these blood samples will be ~3 mL.

At the end of all of the visits participants will be provided with a breakfast. They will be invited to select something of value up to $10 from a menu of a local vendor on Campus West (e.g. Rocky Mountain Bagels). The research staff will collect and deliver the breakfast to the participant for enjoyment while in the lab.

i) **Please take a moment to identify which procedures outlined above are experimental and which are considered standard of care or established practice for the condition or situation in this area.**

All of the procedures are standard research procedures, and all have been previously approved by the IRB for currently active and previous protocols (please refer to protocols: 19-8667H, 20-10278H, 19-9577H, 17-7577H, 13-4282H, 10-2202H, 09-1125H and 08-610H).

b) **Explain who will conduct the procedures, where, and when they will take place. Indicate the frequency and duration of visits/sessions as well as the subject's total time commitment for the study. Include how the data will be collected (i.e. in person or online).**

The procedures will be conducted by the investigator (Bell) and/or by trained members of the research team (including staff and students): Taylor Ewell (CITI 8/19/2018), Keiran Abbotts (CITI, 7/17/2019), Natasha Williams (CITI 2/1/2018), Kole Harms (CIITI 5/21/2019), Matthew Bomar (CITI 2020) and Jordan Rebik (CITI 8/20/2020), and Hannah Butterklee (CITI December 2020).
All procedures will take place in the Human Performance Clinical Research Lab in the Department of Health and Exercise Science. There will be eight visits. Visit 1 will last up to 0.5 hours. Five of the visits will last 4.5 hours each. Two of the visits will last 5.5 hours each. The total time commitment for a participant will be up to 34 hours distributed over approximately 10-12 weeks to allow lots of time between each visit and facilitate flexible scheduling.

i) **Indicate if the instruments used are in the public domain or provide appropriate documentation of permission to use each scale.**

Not applicable

c) **For school-based activities where class time is used, describe in detail the activities planned for nonsubjects and explain where both subjects and nonsubjects will be located during the activities.**

Not applicable

d) **State if deception will be used. If so, provide a rationale and describe debriefing procedures. Submit a debriefing script in attachments section**

No deception will be used in this study.

e) **Will audio or video taping of individuals occur? Will photographs of individuals be taken? Describe what will become of the tapes/photographs (e.g., shown at scientific meetings, erased, etc.).**

No audio or video taping will be conducted.

f) **Will the proposed research involve the use of existing, identifiable data/specimens?**

- i. **Yes, this research study only involves the analysis of existing, identifiable data/specimens.**
- ii. **Yes, one of the research activities involved in this research includes the analysis of existing, identifiable data/specimens.**
- X iii. **No, there are no research activities proposed that involve existing, identifiable data/specimens.**

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* * * Background and additional procedures * * *

4. Background and additional procedures

a. **Relevant Background: Discuss the present knowledge, appropriate literature and rationale for conducting the research. Include the rationale for the selected subject population.**

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The growing use of CBD by Americans has outpaced the research. It is of paramount importance to public health to fully understand the charactertistics of CBD absorption and bioavailability, to empirically investigate some of the claims made by unscrupulous CBD manufacturers, and to recognize some of the potential health and safety concerns as they pertain to CBD use. Relevant literature and examples of some of our initial work in this area have been attached to this application.
The selected population consists of healthy adults with a body mass index greater than 25.0 kg/m^2. That is, adults who are considered to be heavier than recommended. We are recruiting from a broad human population because CBD has a diverse range of users and uses. We are excluding individuals that are at most risk of harm from CBD ingestion (fetuses, breastfed babies, children, and those with certain medical conditions or taking specific medications that might have negative interactions with CBD).

b. **Do any of the following apply.**

i. **Will subjects be audio recorded?** N

ii. **Will subjects be videotaped?** N

iii. **Will subjects be photographed?** N

If yes to i, ii or iii, explain the collection process and use in the context of this research of such media

(Explicit consent must be obtained for use of these methods for Expedited and Full Board studies.)

---

* * * Subject Population (a-f) * * *

5. Subject Population

a) **How many subjects to you intend to enroll and/or how many subject records to you intend to access?**

i. **At CSU**

# of subjects (required, enter 0 if not prospectively enrolling) 25

# of records or data (required, enter 0 if not accessing existing data records) 0

ii. **At all sites (if cooperative or multi-site research)** X **N/A**

# of subjects (if selected, this is required. Enter 0 if not prospectively enrolling)

# of records or data (if selected, this is required. Enter) if not accessing existing data records)

b) **Inclusion and Exclusion Criteria (e.g., Participants must have 20/20 vision, Participants must be 30-45 years of age, etc.) This should match your screening, consent, and recruitment materials.**

i. **Identify inclusion criteria.**

Participants must be greater than 18 years of age, weigh more than 110 lbs, have a body mass index greater than 25 kg/m^2, be free of any gastrointestinal or metabolic diseases, and be able to refrain from use of any Cannabis or cannabis-containing products for three days prior to participating in the study.

ii. **Identify exclusion criteria.**

Individuals that are less than 18 years of age, are pregnant or breastfeeding, have known food allergies, or have been diagnosed with any autoimmune disorders or with compromised immune function, Celiac disease, inflammatory bowel diseases, gastrointestinal cancers, diabetes, or HIV. In addition, anyone who has ever had an adverse reaction to ingesting Cannabis spp. or cannabis-containing products (including, but not limited to, marijuana, CBD oils, or CBD/THC containing food products) or is taking any of the following medications will be excluded as these may have negative interactions with CBD: steroids, HMG-CoA reductase inhibitors, calcium channel blockers, antihistamines, HIV antivirals, immune modulators, benzodiazepines, antiarrythmics, antibiotics, anesthetics, antipsychotics, antidepressants, anti-epileptics, beta blockers, proton pump inhibitors, NSAIDs, angiotension II blockers, oral hypoglycemic agents, and sulfonylureas.

c) **What is the rationale for studying the requested group(s) of participants?**

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CBD is sold as a dietary supplement and often taken as an anti-inflammatory supplement. Therefore, we are looking to study its effects in a generally healthy population. We want to minimize potential for adverse effects and thus have excluded populations that have the highest likelihood of negative interaction, such as those on prescription medications that are metabolized by Cyp450 or individuals that may have issues with absorption. We are not excluding habitual users of CBD or other cannabis-containing products, as these individuals are our target population regarding information on absorption and excretion. Furthermore, our previous studies enrolled both habitual users as well as those that do not regularly take cannabis products and these individuals had similar baseline levels of CBD in the blood after a 3 day abstinence period as well as similar clearance from blood after the single dose.

d) State if any of the subjects are students, employees, or laboratory personnel. Please explain how subjects will be protected from coercion and undue influence N/A

If any of the subjects are students, employees, or laboratory personnel they will be protected from coercion and undue influence. They will complete the same Informed Consent as all other non-students, non-employees, and non-laboratory personnel, thus they will be given the following information in writing:
"For questions regarding the rights of research subjects, any complaints or comments regarding the manner in which the study is being conducted, contact the CSU Institutional Review Board at: RICRO_IRB@mail.colostate.edu; 970-491-1553."
And,
"Your participation in this study is voluntary. You may refuse to participate in this study or in any part of this study. You may withdraw at any time without prejudice to your relations with CSU. You are encouraged to ask questions about this study at the beginning or any time during the research study."

e) Please describe the expertise you have, or have access to, which prepares you to conduct research in this location and/or with this subject population, including specific qualifications (e.g., relevant coursework, background, experience, and training). Also, explain your knowledge of local community attitudes and cultural norms and cultural sensitivities necessary to carry out the research (e.g., differences with U.S. culture).

Our laboratory carries out numerous human clinical studies and we have a well equipped clinic with specifically trained personnel, including a GCP-certified clinical coordinator. We regularly collect and process blood both by venipuncture and through IV catheters. The current project will be our third human study related to cannabinoids.
We are currently conducting other studies where these and other procedures are being carried out. We regularly recruit from among healthy individuals at the university and from within the community. The community, in general, is receptive to research and we do not anticipate any issues with recruitment of this small sample.

---

* * * Subject Population (g-j) * * *

5. Subject Population

f) Will bilingual or multilingual subjects be recruited? Y

g) Will non-English speaking subjects be recruited? N

If yes, state language(s) spoken (other than English):

h) Will subjects be less than 18 years of age? N

i) Describe any planned screening procedures. Attach your screening document(s) (e.g., health history questionnaire) in the Attachment Section (#16).

Potential participants will be screened prior to consent and enrollment. We will ask a series of questions in a phone or in-person interview (see attached). All willing individuals that meet the enrollment criteria will be eligible to participate.

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* * * Recruitment Process, Subject Compensation and Costs * * *

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6. Recruitment Process:

a) Describe the step-by-step procedures for identifying and recruiting potential research subjects or requesting pre-existing data or materials. All recruitment materials must be uploaded in Attachment section, and have IRB approval prior to use.

- **List any specific agencies or institutions that will provide access to prospective subjects.**
- **Identify who will contact prospective subjects and how.**

We will recruit individuals through word of mouth and by email (ie. CSU listservs, CSU clubs such as the Holistic Health Alliance and Food and Nutrition Club) and through social media platforms such as NextDoor and Facebook.

b) Planned Subject Identification Methods:

	N/A	X	Direct advertising
	Chart/database review		Living conditions (e.g., nursing home residents)
	Class participants	X	From PI's own practice/clinic/class
	Circumstance (e.g., homelessness)		Referrals
X	Organization mailing lists		CSU Subject Pool
X	Other (please specify):		social media platforms

c) Planned Recruitment Materials/Methods:

	N/A	X	Flyers/posters
	Phone Scripts		Letters to providers/schools/organizations
	Television ads		Newspaper ads
	Letters to prospective subjects		Radio ads
	Oral Scripts		PowerPoint presentations
X	Internet ads/postings	X	Email
X	Face to face interactions		CSU Subject Pool
	Other (please specify):		

(All advertising must be submitted for review in its final printed/recorded form)

Note: Attach copies of ALL recruitment materials in the attachment Section

7. Subject Compensation and Costs:

a) Will subjects receive compensation for participation? Y

Total amount (in dollars or equivalent) 520

b) Form of Compensation:

X	Cash		Raffles/lotteries
	Check		Course/extra credit
	Gift card/certificate		Reimbursement only
	Voucher		Other (please specify)

c) Describe the remuneration plan (Include when subjects will be paid, whether payment will be prorated and whether a 1099 will be issued.)

As per the Informed Consent, participants will receive the following information:
You may receive up to $520 for your participation in this study. Your remuneration will be as follows:
You will not receive remuneration for completing visit 1. When you complete visit 2 you will receive $40. When you complete visit 3 you will receive $50. When you complete visit 4 you will receive $60. When you complete visit 5 you will receive $70. When you

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complete visit 6 you will receive $80. When you complete visit 7 you will receive $90. When you complete visit 8 you will receive $100. If you complete all visits without needing to reschedule (unless due to extreme inclement weather and/or laboratory equipment malfunction, etc.) you will receive a BONUS of $15, and if you arrive at the lab within 10 minutes of the original scheduled time for each visit, you will receive an additional BONUS of $15.

d) For raffles include the number of prizes, nature and value of each prize.If possible, include odds of winning.

Not applicable.

e) If extra course credit is offered be sure to address the alternative means by which students can accrue extra course credit should they not wish to participate in the study.

Not applicable.

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* * * Risks * * *

8. Risks (Input N/A if not applicable)

US Department of Health & Human Services (HHS) Regulations define a subject at risk as follows: "...any individual who may be exposed to the possibility of injury, including physical, psychological, or social injury, as a consequence of participation as a subject in any research, development, or related activity which departs from the application of those accepted methods necessary to meet his needs, or which increases the ordinary risks of daily life, including the recognized risks inherent in a chosen occupation or field of service."

a) PI's evaluation of the overall level of Risk

Minimal Risk: probability and magnitude are not greater than everyday living OR are encountered in daily or routine medical, dental or psychological exams

X Greater than minimal

b) Describe all known risks or discomforts associated with study procedures. Hint: Any risks identified here should be consistent with risks you will disclose to participants in the consent process.

1) Physical well-being

Body Composition (DEXA) Scan – The risks associated with the DEXA are very low. The maximum radiation dose you will receive in this study is less than 1/1000th of the federal and state occupational whole body dose limit allowed to radiation workers (5,000 mrem). Put another way, the maximum dose from any scan we utilize with this DEXA ranges from 1.2 mrem (Whole body scan) to 12.2 mrem (for several of the regional scans, such as lumbar, femur, and forearm scans). The average annual background radiation you already receive is at least 620 mrem/year. The more radiation you receive over the course of your life, the more the risk increases of developing a fatal cancer or inducing changes in genes. The radiation in this scan is not expected to significantly increase these risks, but the exact increase in such risks is not known. There are no discomforts associated with this procedure. Women who are or could be pregnant should receive no unnecessary radiation and should not participate in this study.

CBD - There may be side effects of CBD consumption, including nausea, fatigue and irritability. In addition, CBD can increase the level in your blood of the blood thinner coumadin, and it can raise levels of certain other medications. It is important to disclose any medications that you are taking to study personnel.

Venous Catheter – Participant may feel some discomfort when the needle is inserted and taped to the hand or wrist. In about 1 in 10 cases, a small amount of bleeding will occur under the skin that will cause a bruise. The risk of forming a blood clot in the vein is about 1 in 100, and the risk of significant blood loss is 1 in 1,000. There is also a risk of minor and temporary physical and psychological distress associated with the collection of blood samples, including fainting. In very rare cases an infection can occur at the site of needle insertion.

Resting metabolic rate - some people may feel claustrophobic while lying under the clear plastic ventilated hood.

2) Psychological well-being

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N/A

3) Economic well-being, including employability

N/A

4) Social well-being (reputational risks)

N/A

c) Describe the procedures or safeguards in place to protect against or minimize potential risks (e.g., referral to psychological counseling resources).

All participants must be a minimum of 18 years old and 110 lbs to reduce adverse risks associated with the blood collection. Individuals that are at risk for adverse reactions due to health concerns or medication use will be excluded from the study as will those unable to tolerate a prolonged period of fasting (ie. people with diabetes). Participants will remain semi-supine in a hospital bed during the course of the study to minimize dizziness, fainting, or falls due to blood collection. Only trained personnel will place the catheter, monitor IV fluids, and collect blood samples. All materials are purchased from certified medical suppliers, are for single use only, and are discarded appropriately after use.
The PI will notify the CSU IRB to report any adverse event as soon as possible. A copy of the adverse events report form will be made available to IRB manager.
All study personnel are trained in CPR and basic first aid procedures. We regularly conduct the study procedures and do not anticipate any issues in our healthy target population.

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* * * Benefits * * *

9. Benefits: Benefits of the research may not include any direct benefits to the participants, but must have benefits of the research for societal impacts, future research, etc.

a) Discuss any potential benefits that would justify involvement of subjects in this study.

i. Direct benefits to subjects (if applicable)

No direct benefits to participants.

ii. Indirect benefits to society

Currently state and federal laws have begun to permit the sales of CBD for medical uses, although little is known about CBD bioavailability via various administration routes and there are few scientific studies to support purported benefits. This study will examine the bioavailability of orally administered CBD, explore potential metabolic interactions, and investigate the acute effect of CBD on liver health.

b) Please describe how the benefits of the research justify the likely risks to participants in your study. If your study presents greater than minimal risk, there should be benefits to the research that outweigh exposing people to such risks.

The risks of participation in the study are minimal compared to the benefits gained from a better understanding of the bioavailability of CBD.

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* * * Procedures to Maintain Confidentiality * * *

10. Procedures to Maintain Confidentiality

Which of the following types of data will you work with:

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Identifiable Information is considered to be identifiable when it can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems, or when characteristics of the information obtained are such that by their nature a reasonably knowledgeable person or investigator could ascertain the identities of individuals. Therefore, even though a dataset may have been stripped of direct identifiers (names, addresses, student ID numbers, etc.), it may still be possible to identify an individual through a combination of other characteristics (e.g., age, gender, ethnicity, and place of employment).

Anonymous Data are anonymous if no one, not even the researcher, can connect the data to the person who provided it--no identifying information is collected from the individual. Investigators must be aware, however, that even if no direct identifiers (name, address, student ID, etc.) are collected, identification of a participant may be possible from unique individual characteristics (indirect identifiers). For example, a participant who is a member of a certain ethnic group or who was studied because of distinctive personal accomplishments or medical history might be identifiable from even a large data pool.

De-identified If the dataset has been stripped of all identifying information and there is no way that it could be linked back to the subjects from whom it was originally collected (through a key to a coding system or by any other means). Note: This also applies if the source of the data is identifiable but the data collected is not.

X Coded This refers to data that have been stripped of all direct subject identifiers, but in this case each record has its own study ID or code, which is linked to identifiable information such as name or medical record number. The linking file must be separate from the coded data set. This linking file may be held by someone on the study team (e.g. the PI) or it could be held by someone outside of the study team (e.g. researcher at another institution). A coded data set may include limited identifiers under HIPAA. Of note, the code itself may not contain identifiers such as subject initials or medical record number.

a) If information derived from the study will be provided to the subject's personal physician, a government agency, or any other person or group (other than the research team), describe to whom the information will be given and the nature of the information, if applicable. N/A

b) Explain how you will protect subjects' privacy. Note: Privacy refers to persons and their interest in controlling the access of others to themselves. For example, based on their privacy interest's people want to control:

- The time and place where they give information.
- The nature of the information they give.
- The nature of the experiences that are given to them.
- Who receives and can use the information.

For example, persons might not want to be seen entering a place that might stigmatize them, such as a pregnancy-counseling center that is clearly identified as such by signs on the front of the building. Please keep this definition in mind as you respond to this item.

Participants will be given the opportunity to respond to the screening questionnaire via email, from a location of their choosing, or in person, in a private interview room in the Human Performance Clinical Research Lab.
The information provided by the participants will include pertinent medical history. We believe the risk/benefit of providing this information is appropriate in order to identify potential contra-indications for study participation (see exclusion criteria) and minimize the risk of an adverse event. All study visits will take place in a private/secure research space within the Human Performance Clinical Research Lab; only members of the research team will have access to this space during the subjects' visits.

c) Describe how you will maintain the confidentiality of subjects' information. Note: Confidentiality pertains to the treatment of information that an individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others (without permission) in ways that are inconsistent with the understanding of the original disclosure. Please keep this definition in mind as you respond to this item.

Participants will be identified only on a signed consent form and initial screening form that will be kept locked and separate from other research data. Each subject will be assigned a randomly generated 8-locked and separate from other research data. Each subject will be assigned a randomly generated 8-character code (e.g. 12698afd) that will be used to identify them in association with all other research data and blood or tissue samples. Records identifying individuals will be kept in Dr. Bell’s office/laboratory in a locked cabinet and will be destroyed (shredded) following completion/publication of the project.

d) Who will have access to study records or specimens? (Please identify specific team members by name.)

All members of the PI's research team will have access to the study records and specimens. As per the information already provided in 3b, the research team consists of the PI, and Taylor Ewell, Keiran Abbotts, Natasha Williams, Kole Harms, Matthew Bomar, Jordan Rebik, and Hannah Butterklee.
De-identified study data and biological samples will be available for processing by the Analytical Toxicology Laboratory at CSU.

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Analyzed data will be provided to the sponsor as well as made public in peer-reviewed publications.

e) **Please explain how the data is being managed, stored, and represented? Describe your method of securing and managing potentially sensitive data. CSU has resources at Data Management Services at CSU Libraries. Upload your Data Management Plan (DMP) in the attachment section. This section should be a brief description of that plan.**

As per advice provided by the IRB during previous protocol reviews, we will employ the 3-2-1 approach to data management.

f) **If you plan to use existing data, records or specimens, what is the source of the data/records/specimens, and how will you access them?NOTE: "Existing" means data or specimens collected (i.e., on the shelf) prior to the IRB application submission. It includes data or specimens collected for research and non-research activities.**

N/A

g) **How will subjects be asked to provide their permission for release of identifiable data collected as a part of this proposed research (e.g., pictures, recordings, responses to research questions), now or in future? Explain and include appropriate statements in consent materials.45 CFR 46 requires specific boilerplate language related to this, please visit the CSU templates for language.**

N/A

g) **If using existing data/biological specimens, will the researchers have access to a code linking the data to personally identifiable information?**

N/A

h) **If the data is coded, explain where the key to identifiers will be stored, how it will be protected, and who will have access to it.**

Participants will be identified only on a signed consent form and initial screening form that will be kept locked and separate from other research data. Each subject will be assigned a randomly generated 8-character code (e.g. 12698afd) that will be used to identify them in association with all other research data and blood or tissue samples. Records identifying individuals will be kept in Dr. Bell's office/laboratory in a locked cabinet and will be destroyed (shredded) following completion/publication of the project.

i) **[MULLING]]]Explain why, where, in what format, and for how long data/specimens will be retained.If you intend to deposit your research data/specimens into a repository for future use, please identify that here. Please outline any plans for submitting data for open source access here, as well. ORIf you feel you will not be asked to submit data for open source or do not intend to archive your data per CSU recommendations, please specify your procedures for management of data and destruction.**

Study data and consent documents will be kept for a minimum of three (3) years after the completion of the study by the PI. Data records will be kept in Dr. Bell's office/laboratory in a locked cabinet. Only the research team will have direct access to the data. If required, data maybe released to governmental entities authorized to inspect research records. Specimens will be kept in a secure space within the Human Performance Clinical Research Lab; only members of the HPCRL will have access to this space.

j) **Will the identifying information be destroyed at a specific date? How will this be destroyed? [definition: destruction of information guidance/link here]**

Study data and consent documents will be kept for a minimum of three (3) years after the completion of the study by the PI. Following which hard (paper) copies will be shredded, and electronic records containing identifying information deleted.

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* * * Consent Information * * *

11. What is Consent? The consent process is intended to fully inform participants of their involvement in your research project. This should describe what a participant will be expecting when they are involved in your activities. Nothing should surprise them. The basic elements of informed consent can be found at 46.116This may include, but not limited to screening consents, consent scripts, main study consent, reconsenting materials. Informed consent can be obtained through varied processes: Consent (formal,

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reconsenting materials. Informed consent can be obtained through varied processes: Consent (formal, signed consent)Waiver of Documentation (verbal, cover letter, 'Click to Consent' or implied consent)Waiver (waiver of parental permission or participant consent)Alteration (formal, signed consent with deception or exempt qualifying research)Debriefing (post participation providing addt'l information)Screening ConsentPlease label each item appropriately so your IRB reviewers understand what purpose/population each document is aiming to address.

11 a & b apply ONLY to Exempt applications.NOTE: If you are completing an Exempt application, please upload all your consent, recruitment, and supporting documentation in the Attachments section of the application.

a) **How will subjects be informed of procedures, intent of the study, and potential risks to them?**

N/A

b) **How will subjects be informed they may withdraw at any timewithout penalty?**

N/A

Note: Attach, in the Attachments Section, written and/or verbal instructions the subject will receive.

See sample consent forms at https://www.research.colostate.edu/ricro/irb/templates//

Please provide consent process background information below.

Informed Consent

Title	Consent Type	Attached Date	Submitted Date
Consent 21-10634H 03182021	Consent	03/19/2021	

* * * Assent Background * * *

12. Assent Background: What is assent? Assent is a process of soliciting affirmative acknowledgement from minors (or vulnerable populations who are unable to give adequate consent) to participate in your research. Assent can be obtained by various means appropriate to the population. Per 46.408(a), consider age, maturity, and psychological state of the children involved in your research as you develop an assent procedure. Even the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which a consent may be waived (46.116).

(Complete if applicable)

Assent Procedure: Unlike the regulatory required elements of consent, assent elements are not defined by regulations. Assent is the affirmative acceptance to participate in research and should still be solicited in a population-specific manner. Assent can be a form or script of information that will be conveyed to the participant about the study. Assent language should be at a level understandable to the participant and be accompanied with adequate discussion. If the study includes a broad range of capacity to consent (whether age or cognition), more than one assent procedure may be needed (i.e., an assent form suitable for a 17 year old is not usually suitable for a 7 year old child).

Assent Waiver: In some cases, all or some of your participants may be incapable of providing affirmative assent to participate (based on age or diminished intellectual capacity). In such cases, the IRB may waive the requirement for assent.

See sample consent/assent forms at https://vpr.colostate.edu/ricro/irb/templates/

Upload your appropriate assent documentation below. If there is more than one assent process, please properly label and identify to minimize

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confusion during IRB review.

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* * * HIPAA * * *

13. Health Insurance Portability and Accountability Act (HIPAA)

If you are using PHI and this page is not active you must return to the General Checklist and check the box regarding the use of PHI in this research.

The HIPAA Privacy Rule establishes the right of an individual to authorize a covered entity, such as health plan, health care clearinghouse or health care provider, to use and disclose his/her Protected Health Information (PHI) for research purposes.

The Privacy Rule defines the elements of individual information that comprise PHI and establishes the conditions under which PHI may be used or disclosed by covered entities for research purposes. It also includes provisions to allow an individual's PHI to be disclosed or used in research without the person's authorization (i.e., IRB Waiver of HIPAA Requirement Authorization).

Is Your Research Covered by HIPAA's Privacy Rule?

Protected Health Information (PHI) is health information with one or more of the following identifiers. For more information see: http://privacyruleandresearch.nih.gov/clin_research.asp or consult HIPAA Privacy Rule for Research

Research which involves the use of de-identified data is exempt from HIPAA requirements. In order to be de-identified data. NONE of the subject identifiers listed below can be collected, used, reviewed, recoded, accessed or disclosed.

Please review the following list and indicate if any of the information will be collected from any medical records for the purpose of this research project.

1. Names
2. Social Security Numbers
3. Telephone Numbers
4. All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if according to the current publicly available data from the Bureau of the Census;
   i. The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and
   ii. The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
5. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all wages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
6. Fax Numbers
7. Electronic Mail Addresses
8. Medical Record Numbers
   - You must attach a data collection sheet identifying the data points being collected from the MRN
9. Health Plan Beneficiary Numbers
10. Account Numbers
11. Certificate/License Numbers
12. Vehicle Identifiers and Serial Numbers, including License Plate Numbers
13. Device Identifiers and Serial Numbers
14. Web Universal Resource Locations (URLs)
15. Internet Protocol (IP) Address Numbers
16. Biometric Identifiers, including Finger and Voice Prints
17. Full Face Photographic Images and any Comparable Images
18. Any other unique identifying number, character, or code (note this does not mean the unique code assigned by the Investigator(s)

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to code the research data)

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* * * Drugs and Devices * * *

14. Drugs and Devices: Please provide Investigator's Brochure or Package Inserts of Drugs in the Attachment Section. Please describe the dosing amounts (minimum & maximum) and schedule of all drugs in the Protocol Procedures.If this section is required due to your selection of ClinicalTrials.gov on the General Checklist, and your study does NOT include FDA-regulated drugs or FDA-regulated devices, please type: Not Applicable in the required fields.

Drugs

Name	IND Number (if applicable)	Type of Research
none	N/A	IND-Exempt

Drugs

Name* none
IND Number (if applicable) N/A
Type of Research* IND-Exempt

Label

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* * * Potential Conflict of Interest * * *

15. Potential Conflict of Interest

Conflict of Interest and the definitions related to the Conflict of Interest Policy and the following questions, please refer https://www.research.colostate.edu/ricro/coi/

Conflict of Interest: Please check Yes or No for each item below.

a) N Does the research involve a drug, device, or biological invented by you, an immediate family member or other Research Personnel?

b) N Is the research sponsored by an entity with which you, an immediate family member, or other Research Personnel have a paid consulting or advising relationship?

c) N Will you, members of your immediate family, or other Research Personnel receive special compensation or increased compensation if the research generates a favorable outcome?

d) N Will you, members of your immediate family, or other Research Personnel receive any money, gift or anything of monetary value above and beyond the actual costs of enrollment, conduct of the research, and reporting on the results, including, but not limited to, finders fees, referral fees, recruitment bonuses, and an enrollment bonus for reaching an accrual goal or similar types of payments?

e) N Do you, members of your immediate family or other Research Personnel have any other interests or relationships (including volunteer services) that might constitute a conflict of interest or an appearance of conflict of interest in connection with the research project?

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research project?

f) N Will the payment you receive for services provided during the conduct of the research (e.g., investigator and Research Personnel time and tests) be inconsistent with fair market value for those services?

Significant Financial Interest: Please check Yes or No for each item below.

g) N Will you, your immediate family members or other Research Personnel receive salaries, royalties and/or other payments for services (e.g., consulting fees, honoraria, research design, management position, independent contractor, service on advisory or review committees, board membership seminars, lectures or teaching engagements when totaled together exceeded $5,000 during the previous 12 months or are expected to exceed $5,000 over the next 12 months)? This excludes reasonable costs of conducting the research, as specified in the research agreement.

h) N Do you, your immediate family members, or other Research Personnel hold any ownership interests including stocks, bonds, or stock options that exceed $5,000 and/or that constitute more than a five percent (5%) ownership interest in the sponsoring organization? This does not include any interests held solely by reason of investment in a business by a mutual, pension or other institutional investment fund over which the investigator and/or his or her immediate family do not exercise day-to-day control of investment decisions.

Minimizing Risks and Disclosure to Subjects

i) Y Have you disclosed any actual, potential or perceived conflicts of interest in the consent form? Research Personnel are required to disclose all such conflicts to all research participants in the research consent form.

j) **What steps, if any, have you taken or will you take to manage the conflict of interest and minimize the risks associated with any actual, potential or perceived conflicts of interest arising out of this research?**

The CBD formulations under investigation will be manufactured by Caliper Foods. Caliper Foods will sponsor the research. Caliper Foods will not be involved with any of the data/sample analysis. This information has been disclosed in the Consent Form.

If you checked Yes to any statement (a-h, except f) above, please identify the research team member(s) below and provide details concerning the potential conflict of interest.

By submitting this form, you are attesting that you have read the Client HRPP Policy on Conflict of Interest and agree to abide by its terms. You will update this disclosure form when new or changes in conflict of interest arise, and that you will comply with any conflict management plan required by the Institutional Review Board (IRB) to manage, reduce, or eliminate any actual or potential conflict of interest for the duration of the research.

Link to CSU's Conflict of Interest Policy: https://vpr.colostate.edu/ricro/coi/.

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* * * Attachments * * *

16. Attachments: Attach all relevant documentation to your research in this section. Any documentation that will be seen by a participant must be reviewed and approved by the IRB. This includes multiple communications, tools, instruments, etc.Please label each item appropriately so your IRB reviewers understand what purpose/population each document is aiming to address.

Attach relevant documents here. These could include:

- **Grant proposal for congruency review. Please adequately reference in the Funding section.**
- **Collaborating Investigator's IRB approval and approved documents**
- **Conflict of Interest information**
- **Debriefing Script; Grant/Sub-contract**
- **HIPAA Authorization Form from HIPAA-covered entity**
- **Interview/Focus Group Questions**
- **Investigator's Brochure**
- **Letters of Agreement/Cooperation from organizations who will help with recruitment**

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- Methodology section of associated Thesis or Dissertation project
- Questionnaires
- Radiation Control Office approval material
- Recruitment Material (e.g., flyers, email text, verbal scripts)
- Sponsor's Protocol; Surveys
- Other files associated with the protocol (you can upload most standard file formats: xls, pdf, jpg, tif, etc.)

Please be sure to attach all documents associated with your protocol. Failure to attach the files associated with the protocol may result in this protocol being returned to you for completion prior to being reviewed.

Students: Be sure to attach the Methods section of your thesis or dissertation proposal. If this protocol is associated with a grant proposal, please remember to attach your grant and reference in the funding section.

To update or revise any attachments, please delete the existing attachment and upload the Tracked Changes version and Clean revised document for review.

Document Type	Document Name	Attached Date	Submitted Date
Recruitment Material (e.g., flyers, email text, verbal scripts)	21-10634H email recruitment	03/03/2021	03/03/2021
Recruitment Material (e.g., flyers, email text, verbal scripts)	21-10634H Recruitment	03/03/2021	03/03/2021
Other, supplemental information	Comparison of Five CBD Preparations	03/03/2021	03/03/2021
Other, supplemental information	CBD Pharmacokinetics Anti-Inflammatory	03/03/2021	03/03/2021
Other, supplemental information	Phytocannabinoids NAFLD Treatment	03/03/2021	03/03/2021
Other, supplemental information	Cannabidiol and Abnormal Liver Chemistries in Healthy Adults	03/03/2021	03/03/2021
Grant/Sub-Contract	Sponsor contact info	03/18/2021	03/18/2021
Grant/Sub-Contract	Re_ Bell_KR149100_Caliper foods	03/18/2021	03/18/2021
Grant/Sub-Contract	149100 Bell Caliper Foods	03/18/2021	03/18/2021
Grant/Sub-Contract	149100 scope of work	03/18/2021	03/18/2021
Questionnaire/Survey	21-10634H Screening questionnaire 03182021	03/18/2021	
Other Protocol Material	CALIPER TS-001, T-P-S-10_ Rev 10.0	03/19/2021	
Investigator's Brochure	[DRAFT] of CALIPER TS-000, Isolate_ Rev 1.0	03/23/2021	03/23/2021

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Investigator's Brochure	[DRAFT] of CALIPER TS-000, Oil Based Tincture_ Rev 1.0	03/23/2021	03/23/2021
Investigator's Brochure	[DRAFT] of CALIPER TS-000, T-P-MA-10_ Rev 1.0	03/23/2021	03/23/2021
Investigator's Brochure	[DRAFT] of CALIPER TS-000, T-P-SA-10_ Rev 1.0	03/23/2021	03/23/2021

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* * * Obligations * * *

Obligations

The Principal Investigator is ultimately responsible for the conduct of this project.

Obligations of the Principal Investigator include the following:

Provide all subjects a copy of the signed consent form, if applicable.

Modifications - Changes in any aspect of the study (for example, project design, procedures, consent forms, advertising materials, additional key personnel or subject population) will be submitted to the IRB for approval before instituting the changes.

Training - Human subject training certificates, including those for any newly added personnel, will be provided for all key personnel.Training must be updated every three (3) years.

Final Report - The IRB will be notified when the study is complete.

I certify that I have reviewed this application, including attachments and that all information contained herein is accurate to the best of my knowledge. I agree to report any substantive changes to the information contained in this application immediately to the CSU IRB.

I agree to not enroll any subjects or collect any data intended only for research use prior to issuance of an IRB approval.

I agree to manage and maintain all of my research records, including consent retention, for at least three (3) after the close of this study or longer per sponsor requirement.

I understand that I am fully responsible for the execution and management of this study and that I am responsible for the performance of any subinvestigators or key personnel including their adherence to all of the applicable policies and regulations.

This study will not begin until the investigator receives written final approval or determination of exemption.

X **The Principal Investigator has read and agrees to abide by the above obligations.**

Submit the Continuing Review Form in order to maintain active status of the approved protocol. This form must be submitted to the IRB prior to the date of expiration.

Submit the Protocol Violation Form to report protocol Deviations/Violations or the Event Reporting Form to report Adverse Events (AEs) or Unanticipated Problems that occur in the course of the protocol.

X **The Principal Investigator has read and agrees to abide by the above obligations.**

Please click "Check for Completeness" to your left to continue to the next step. If the protocol is complete and ready for submission, please click "Submit Form" to your left to submit your protocol for IRB Review.

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* * * IRB Use Only * * *

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Assigned to :

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* * * Event History * * *

Event History

Date	Status	View Attachments	Letters
03/01/2021	NEW FORM CREATED		
03/03/2021	NEW FORM SUBMITTED	Y	
03/04/2021	NEW FORM PANEL ASSIGNED		
03/11/2021	NEW FORM REVIEWER(S) ASSIGNED		
03/16/2021	NEW FORM Comments Received (Cycle 1)		
03/16/2021	NEW FORM Comments Received (Cycle 1)		
03/17/2021	NEW FORM Comments Received (Cycle 1)		
03/18/2021	NEW FORM Comments Received (Cycle 1)		
03/18/2021	NEW FORM Comments Sent (Cycle 1)		
03/19/2021	NEW FORM Responses Received (Cycle 1)		
03/23/2021	NEW FORM Responses Sent (Cycle 1)		
03/24/2021	NEW FORM Comments Received (Cycle 2)		
03/24/2021	NEW FORM Comments Received (Cycle 2)		
03/24/2021	NEW FORM APPROVED	Y	Y

ADULT PARTICIPANT INFORMED CONSENT
Department of Health and Exercise Science

Participant Study Title:
Interaction between Cannabidiol, Meal Ingestion, and Liver Function

PRINCIPAL INVESTIGATORS:
Christopher Bell, Ph.D., Associate Professor

GRADUATE AND UNDERGRADUATE STUDENT INVESTIGATOR(S):
Taylor Ewell, Kieran Abbotts, Natasha Williams, Jordan Rebik, Matthew Bomar, Hannah Butterklee, and Kole Harms

SPONSOR:
Caliper Foods: https://www.caliperfoods.life/
Caliper Foods will not be involved with any of the measurements made in this study.

WHAT IF I HAVE QUESTIONS?
For questions or concerns about the study, you may contact Dr. Bell at 970-491-7522 (office) and christopher.bell@colostate.edu. For questions regarding the rights of research subjects, any complaints or comments regarding the manner in which the study is being conducted, contact the CSU Institutional Review Board at: RICRO_IRB@mail.colostate.edu; 970-491-1553.

CONCISE STATEMENT OF STUDY
This study has several different goals: (1) to learn how different formulations of Cannabidiol (CBD) leave the stomach and enter the blood. (2) to learn if eating a meal influences how CBD leaves the stomach and enters the blood. (3) to learn if CBD influences how a meal is digested. (4) to learn if CBD influences the health of the liver. You may be eligible because you are: (1) a healthy adult male or female that is over the age of 18, (2) weigh more than 110 Lbs, (3) and your body mass index (your weight divided by a function of your height) is greater than 25 kg/m^2 (we will calculate this for you). This study will require eight visits; the total number of hours for participation will be 34 hours spread over 10-12 weeks. There are some risks to participating in this study, like exposure to a very small amount of radiation, minor discomfort and/or a bruise during blood sampling, and potential interactions between CBD and any medication you are currently using. We hope that this research will benefit our understanding of how swallowed CBD leaves the stomach and enters the blood, how it interacts with a meal, and if it influences the health of the liver. You can find more details on this study in the body of this consent form. If you are interested in continued discussion about the presentation, we would like to discuss more with you through this consent presentation.

WHAT IS THE PURPOSE OF THIS STUDY?

Cannabidiol (CBD) is an oil extracted from hemp plants and sold commercially as a dietary supplement. Millions of Americans use CBD every day. The increase in the day-to-day use of CBD has outpaced our understanding of how it works, how it is absorbed in the body, and how it might affect how our body works. This study has several different goals: (1) to learn how different formulations of CBD leave the stomach and enter the blood. (2) to learn if eating a meal influences how CBD leaves the stomach and enters the blood. (3) to learn if CBD influences how a meal is digested. (4) to learn if CBD influences the health of the liver.

WHY AM I BEING INVITED TO TAKE PART IN THIS RESEARCH?

You are being asked to participate in the study because you fit these criteria: (1) a healthy adult male or female that is over the age of 18, (2) weigh more than 110 Lbs, (3) your body mass index (your weight divided by a function of your height) is greater than 25 kg/m^2 (we will calculate this for you).

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

The study will take place in the Human Performance Clinical Research Laboratory in the Department of Health and Exercise Science on the Fort Collins campus of Colorado State University.

This study will require seven (7) visits. The first visit will last 30 minutes. Five of the visits will each last 4.5 hours. Two visits will each last 5.5 hours. The exact order of the visits will be random. Ideally, each visit will be separated by 1-2 weeks. The total number of hours for participation will be 34 hours spread over approximately 10-12 weeks.

How Does the COVID19 Outbreak Influence Participation In This Study

Any interaction with people outside of your own home may increase your risk of becoming ill with Covid19. To promote your safety, and the safety of others in our research facility, you will be asked to do the following:

1) The day before each of your visits to the Human Performance Clinical Research Laboratory you will receive an email or text reminding you of your appointment. The reminder will also include a short list of questions specific to symptoms and behaviors linked to Covid19.

2) When you arrive at the Human Performance Clinical Research Laboratory you will be asked several questions specific to Covid19.

3) Every person on the university campus is requested to wear a mask. The Human Performance Clinical Research Laboratory is located on the university campus, thus everyone who visits the facility, including staff and research participants, is also requested to wear a mask. You will be asked to remove your mask during some of the research procedures (detailed below). Whenever you are asked to remove your mask,

you will not be within the vicinity of research staff; that is, the research staff may not be present in the room.

WHAT WILL I BE ASKED TO DO?
If you volunteer to participate in this study, you will be asked to do the following:

SIMPLE BIG DESCRIPTION
You will visit the Human Performance Clinical Research Laboratory on 8 different days. During the 1st visit you will complete a brief questionnaire and undergo measures of body composition. Five of the remaining visits will be almost exactly the same as each other. Two of the remaining visits will be almost exactly the same as each other. During five of the visits you will report to the Human Performance Clinical Research Laboratory in the morning. A small plastic tube and needle will be inserted into a vein in your arm or hand. You will eat or drink a small amount of CBD. Blood will be sampled from the plastic tube in your vein several times over 4-hours. We will measure the amount of CBD in your blood. We will also measure the amounts of substances in the blood that reflect the health of your liver. During two of the visits you will report to the Human Performance Clinical Research Laboratory in the morning. A small plastic tube and needle will be inserted into a vein in your arm or hand. We will measure your resting metabolic rate (the number of calories you burn at rest). You will drink a liquid meal. You will eat or drink a small amount of CBD. Blood will be sampled from the plastic tube in your vein several times over 4-hours. We will measure the amount of CBD in your blood. We will also measure the amounts of substances in the blood that reflect the health of your liver. We will also measure the amounts of substances in the blood that reflect how you absorb food.

DETAILED DESCRIPTION
Visit 1: Screening Visit - Duration: Up to 30 minutes
Questionnaire
You will be asked to answer a number of questions related to your health, any illness you may have or have had, and medications you use or have used in the past. (Duration: less than 15 minutes)

Pregnancy Test
If you are female you will be required to have a sample of your urine tested for the presence of human chronic gonadotropin (HCG), a hormone that indicates whether you may be pregnant. This will require approximately 1 cup of your urine. If you are pregnant or the test indicates that you are pregnant you will not be able to participate in this study. (Duration: 5 minutes)

Body Composition
We will measure how much fat you have in your body using a test called dual energy x-ray absorptiometry (DEXA). The DEXA test requires you to lie quietly on a padded table while a small probe gives off low-level x-rays and sends them over your entire body. This test gives very accurate measurements of your body fat and bone mineral

density. We will also measure the circumference of your waist and hip using a tape measure. (Duration: less than 15 minutes)

Five Visits Not Involving A Test Meal: Up to 4.5 hours each
Each of these five visits will be almost exactly the same. Each visit will last up to 4.5 hours. Ideally, each visit will be separated by approximately 1-2 weeks.

During the 3-days (72 hours) before each visit to the laboratory you will not use any products (e.g. foods, drinks, oils, ointments, smoking or vaping products) that contain CBD. You will be asked to confirm this at the start of every visit.

You will arrive at the Human Performance Clinical Research Laboratory in the morning. You will not eat or drink anything other than water for 12-hours before you arrive. You will be asked to confirm this at the start of every visit.

A small plastic tube will be inserted into a vein in your hand or wrist (i.e. a venous catheter). Saline (a liquid comprised of clean water and a very small amount of salt) will be used to keep the plastic tube from becoming blocked. The plastic tube will remain in your vein for 4-hours. From the plastic tube we will collect a small amount of blood (0.8 teaspoons (5 mL)). We will measure the amount of CBD in your blood.

We will measure your heart rate and blood pressure. To promote social distancing, we will make these measurements using a machine (an automated physiological monitor).

You will be asked to eat/drink 30 mg of CBD. The CBD will be prepared differently for each visit. Sometimes it will be in water, sometimes it will be in oil and water. You will be asked to briefly remove your facemask when you eat/drink the CBD.

We will collect 0.8 teaspoons (5 mL) of blood after 10, 20, 30, 45, 60, 120, 180, and 240 minutes. We will measure the amount of CBD in your blood.

Blood will also be collected and analyzed for circulating factors indicative of liver (and also kidney) function. These substances include alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase, total bilirubin, and blood urea nitrogen. These samples will be taken at time 0, 60 and 240 minutes. Each of these blood samples will be 0.16 teaspoons (~1 mL).

The total amount of blood collected during four of these five visits will be 8 teaspoons (48 mL).

During one of the visits, blood will also be collected for the measurement of sugar (glucose), insulin and triglyceride concentration at time -5, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes. Each of these blood samples will be 0.48 teaspoons (~3 mL). The total amount of blood collected during this one visits will be 14 teaspoons (84 mL).

We will measure heart rate and blood pressure every 30-minutes during your visit. To promote social distancing, we will make these measurements using a machine (an automated physiological monitor).

During the entire visit you will need to sit/lie on our hospital bed (or hospital chair). You will be able to perform light activities, such as watching movies, reading, working on a computer and/or studying. You will be able to chat during the visit, but we will ask you to remain quiet and still when we measure your heart rate and blood pressure. During the heart rate measurements, we will ask you to briefly remove your mask so as not to impede your breathing.

At the end of the visit, you will be provided with breakfast from Rocky Mountain Bagel Works (https://www.rmbagelworks.com/). Your menu choices can be of value up to $10.

Two Visits Involving a Test Meal: Up to 5.5 hours each
Each of these two visits will be almost exactly the same. Each visit will last up to 5.5 hours. Ideally, each visit will be separated by approximately 1-2 weeks.

These visits will be somewhat similar to the Visits Without a Test Meal, but they will include a few extra measurements. For example, in the beginning we will measure your resting metabolic rate (the amount of calories you burn while resting). You will lie on a bed and a clear plastic bubble will be placed over your head. The bubble will be well ventilated and it will collect the gases you breath out. During the measurement you will be asked to lie very still. You will not be allowed to read, write, or watch TV. You will be resting. This measurement will last 45 minutes.

After the measurement you will be given a liquid meal. The meal will be a commercially available drink: Boost Balanced Nutrition Drink; Nestle Health and Science. You can find out more about the drink at this website:
https://www.nestlenutritionstore.com/boost-original.html

The amount of Boost you drink will be related to your resting metabolic rate. People with a higher metabolic rate will drink more Boost than people with a lower metabolic rate. The number of calories in the Boost you are given will be approximately equal to 30% of your total daily calories. Immediately after drinking the Boost, you will be asked to eat/drink 30 mg of CBD or a placebo. A placebo is something that has no effect. You will not be told if you are swallowing the CBD or the placebo until the study is over. You will be asked to briefly remove your facemask when you eat/drink the Boost and CBD.

Immediately after the Boost and CBD ingestion, we will re-measure your metabolic rate using the clear plastic, ventilated bubble. Measurements will last 25 minutes and will be begin at 0, 30, 60, 90, 120, 150, 180, and 210 minutes. At the end of each 25-minute

measurement, the bubble will be removed to provide you with a 5-minute break. During the measurements you will be asked to lie very still. You will not be allowed to read, write, or watch TV. You will be resting.

We will collect 0.8 teaspoons (5 mL) of blood after 10, 20, 30, 45, 60, 120, 180, and 240 minutes. We will measure the amount of CBD in your blood.

Blood will also be collected and analyzed for circulating factors indicative of liver (and also kidney) function. These substances include alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase, total bilirubin, and blood urea nitrogen. These samples will be taken at time 0, 60 and 240 minutes. Each of these blood samples will be 0.16 teaspoons (~1 mL).

Blood will also be collected for the measurement of sugar (glucose), insulin and triglyceride concentration at time -5, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes. Each of these blood samples will be 0.48 teaspoons (~3 mL).

The total amount of blood collected during these two visits will be 14 teaspoons (84 mL).

We will measure heart rate and blood pressure every 30-minutes during your visit. To promote social distancing, we will make these measurements using a machine (an automated physiological monitor).

At the end of the visit, you will be provided with breakfast from Rocky Mountain Bagel Works (https://www.rmbagelworks.com/). Your menu choices can be of value up to $10.

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY?

There may be no direct benefit to you as a participant in this study. However, we hope to learn more about how different formulations of CBD leave the stomach and enter the blood, how CBD interacts with a meal, and if CBD influences the liver.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

Body Composition (DEXA) Scan – The risks associated with the DEXA are very low. The maximum radiation dose you will receive in this study is less than 1/1000th of the federal and state occupational whole-body dose limit allowed to radiation workers (5,000 mrem). Put another way, the maximum dose from any scan we utilize with this DEXA ranges from 1.2 mrem (whole-body scan) to 12.2 mrem (for several of the regional scans, such as lumbar, femur, and forearm scans). The average annual background radiation you already receive is at least 620 mrem/year. The more radiation you receive over the course of your life, the more the risk increases of developing a fatal cancer or inducing changes in genes. The radiation in this scan is not expected to significantly increase these risks, but the exact increase in such risks is not known. There are no discomforts associated with this procedure. Women who are

or could be pregnant should receive no unnecessary radiation and should not participate in this study.

CBD - There may be side effects of CBD consumption, including nausea, fatigue and irritability. In addition, CBD can increase the level in your blood of the blood thinner coumadin, and it can raise levels of certain other medications. It is important to disclose any medications that you are taking to study personnel.

Venous Catheter – You may feel some discomfort when the needle is inserted and taped to your hand or wrist. In about 1 in 10 cases, a small amount of bleeding will occur under the skin that will cause a bruise. The risk of forming a blood clot in the vein is about 1 in 100, and the risk of significant blood loss is 1 in 1,000. There is also a risk of minor and temporary physical and psychological distress associated with the collection of blood samples, including fainting. In very rare cases an infection can occur at the site of needle insertion.

Measurements of metabolism – You may feel a little claustrophobic while lying under the clear plastic bubble. You may become bored because you will not be allowed to do anything stimulating during the measurements.

Covid19 – It is not possible to lower the risk of catching Covid19 to 0%. Our staff have all completed training to try to minimize the Covid19 risk of research participation. This training includes cleaning and dis-infecting research equipment and laboratory spaces, and wearing appropriate protective equipment (e.g. masks, gloves, and lab coats). Research staff will leave the room whenever you are requested to briefly remove your mask.

WILL I RECEIVE ANY COMPENSATION FOR TAKING PART IN THIS STUDY?

You may receive up to $520 for your participation in this study. Your remuneration will be as follows: You will not receive remuneration for completing visit 1. When you complete visit 2 you will receive $40. When you complete visit 3 you will receive $50. When you complete visit 4 you will receive $60. When you complete visit 5 you will receive $70. When you complete visit 6 you will receive $80. When you complete visit 7 you will receive $90. When you complete visit 8 you will receive $100. If you complete all visits without needing to reschedule (unless due to extreme inclement weather and/or laboratory equipment malfunction, etc.) you will receive a BONUS of $15, and if you arrive at the lab within 10 minutes of the original scheduled time for each visit, you will receive an additional BONUS of $15.

WHO WILL SEE THE INFORMATION THAT I GIVE?

All information gathered in this study will be kept as confidential as possible. Your privacy is very important to us and the researchers will take every measure to protect it. Your information may be given out if required by law; however, the researchers will do their best to make sure that any information that is released will not identify you. No reference will be made in written or oral materials that could link you to this study. For this study, we will assign a code to your data so that the only place your name will

appear in our records is on the consent and in our data spreadsheet which links you to your code. Only the research team will have access to the link between you, your code, and your data. All records will be stored in a restricted access folder at CSU for three years after completion of the study. After the storage time, the information gathered will be destroyed.

There are organizations that may inspect research records that may include yours. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor: Caliper Foods
- The CSU financial management team may request an audit of research expenditure, in which only your participating in the research may be shared, but not your research data.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.

If you choose to take part in this study, your blood will be collected. Any identifiers linking you to your blood will be removed. After we remove those identifiers, the blood could be used for future studies or distributed to another research for future research studies without your permission.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

DO I HAVE TO TAKE PART IN THE STUDY?

Your participation in this study is voluntary. You may refuse to participate in this study or in any part of this study. You may withdraw at any time without prejudice to your relations with CSU. You are encouraged to ask questions about this study at the beginning or any time during the research study.

Participant Consent:

Your signature acknowledges that you have read the information stated and voluntarily wish to participate in this research. Your signature also acknowledges that you have received, on the date signed, a copy of this document containing _9_ pages.

_____ _____

Signature of person agreeing to take part in the study Date

_____

Printed name of person agreeing to take part in the study

_____ _____

Name of person providing information to participant Date

_____

Signature of Research Staff providing information to participant

Statistical Analysis Plan
NCT04971837
04/01/2022

All data, unless otherwise stated, are presented as mean and standard deviation. Statistical analyses were performed using dedicated, commercially available software (SigmaStat for Windows 3.5, Systat Software, Inc., Chicago, IL, USA). Differences in pharmacokinetic parameters between CBD formulations for CBD, and the CBD metabolites were explored using one-way analysis of variance (ANOVA) with repeated measures. Tukey's tests were used to further examine the identified main effects. The thermic effect of food was examined using two-way ANOVA with repeated measures comparing energy expenditure across time for the two conditions (i.e., CBD and placebo); respiratory exchange ratio and circulating concentrations of glucose, insulin, and triglycerides were compared in the same way. The thermic effect of food was also examined by comparing the area under the curve (trapezoidal method). Circulating markers of liver and kidney function were compared across time and between CBD formulations using two-way ANOVA with repeated measures and post-hoc Tukey's tests when appropriate. Relations between circulating CBD concentrations and markers of liver and kidney function were explored using Pearson correlations. The level of statistical significance was set at $p < 0.05$.