nature portfolio

Corresponding author(s): Jashvant D. Unadkat
jash@uw.edu
206-543-9434

Last updated by author(s): Dec 28, 2024

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☒	☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	The predictions of THC and 11-OH-THC concentrations in the non-pregnant population were conducted in the commercially available PBPK model software, Simcyp version 22. The predictions for maternal and fetal cannabinoid exposure was conducted using a refined version of our previously developed in-house MATLAB Simulink maternal-fetal-PBPK model (also refined by Shum et al. (2021) Drug Metab Dispos). Our in-house m-f-PBPK model was used since Simcyp does not have the capability to predict metabolite fetal tissue concentrations and we were interested in predicting the 11-OH-THC fetal brain exposure. Additionally, the non-pregnant simulations were verified in MATLAB to confirm that the models were identical between the two software packages. However, we needed to remain with Simcyp for the non-pregnant model as our MATLAB model was not built to predict drug-drug interactions. No software was used for collection of data in the in vivo, observational study. The observed non-pregnant concentration-time profiles used for model verification were obtained by digitization using the WebPlotDigitizer (version 4.6, https://apps.automeris.io/wpd/), unless the individual concentration-time data were available in the publications. All AUCinf calculations for in vivo data were estimated using Phoenix WinNonlin version 8.3.4.
Data analysis	All statistical tests, wilcoxon signed-rank test, were conducted in GraphPad Prism version 8.0.2.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

All data generated or analyzed during this study are included in this published article, its supplementary information, and source data files.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	We did not report sex for pregnant participants in our study as they were all of the female sex. We did report the fetal sex information, where collected, although we do not have enough information whether fetal sex affects fetal cannabinoid exposure. For the non-pregnant model predictions, all demographics including sex distribution was kept consistent with the observed data to which they were compared. As for the m-f-PBPK predictions, all mothers were selected as female sex and and no sex was assigned for the fetus as we did not have any information on how fetal sex affects cannabinoid exposure.
Reporting on race, ethnicity, or other socially relevant groupings	Racial groups were separated as suggested by the NIH guidance on race and national origin: white, african american, american indian, asian/pacific islander, hispanic, and other. Participants self-reported their racial category based on these provided groups. The reported measured and predicted cannabinoid concentrations were not divided based on the racial category.
Population characteristics	Population characteristics such as maternal age, race, and fetal sex were reported, however none of these were considered as covariates in the THC and 11-OH-THC maternal and fetal concentrations.
Recruitment	For the trimester 1/2 study, after patients have received their routine abortion options counseling, consented to their abortion procedure, and had their gestational dating ultrasound, the clinic staff alerted the study coordinator if a patient met the gestational eligibility criteria. The research coordinator then approached the patient in a private room in the clinic with the study talking points and answered their questions. If the patient indicated they are interested in participating, the research coordinator screened them using the study eligibility question screening form. The research coordinator recorded the results of the eligibility screening without any patient identifiers. If the patient was eligible and interested in participating, the research coordinator went over the study consent form in detail with the patient, and answered their questions. If they verbally consented to participate in the research (we have a waiver of signed consent to protect subject privacy) the research coordinator proceeded with the study procedures. All participants also signed the Birth Defects Research Lab consent form for the donation of embryonic and fetal tissue, and this was done prior to screening for this study. Subjects were compensated $40 for completing the survey. For the trimester 3 study, initial contact was made by a trained professional research assistant (PRA) from the OB research team who approached women in person for potential enrollment during or following prenatal clinic visits if they reported marijuana use to a healthcare provider during a prenatal care visit prior to 16 weeks gestation. Alternatively, for social distancing/COVID considerations, the PRA initially contacted women for potential enrollment via MyHealth Connection and telephone calls. The PRA assessed eligibility, consented and enrolled women in the study. A Waiver of HIPAA Authorization was requested for PRAs to examine medical records to identify potential participants. This information was not recorded. This study's investigators also were approved to identify and recommend potential participants via a clinical relationship. Subjects were compensated $100 for enrollment, the prenatal visit, and the blood draw at delivery. The only possible selection bias that we foresee is that, for each study, we recruited individuals from one enrollment site. It is possible that the site that we recruited from is not representative of the greater population.
Ethics oversight	Each study was approved by the respective institutional review board (University of Washington IRB STUDY00008126; Colorado Multiple IRB 19-1757) and performed in accordance with the ethical and legal guidelines.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No sample-size calculation was performed. Our goal was to have 8 subjects with quantifiable THC concentrations in each of the following 6 groups: trimester 1 oral THC consumption, trimester 1 inhalation THC, trimester 2 oral THC consumption, trimester 2 inhalation THC, trimester 3 oral THC consumption, and trimester 3 inhalation THC. The number of 8 subjects was chosen in order to get a representative mean concentration and population variability to verify our maternal-fetal PBPK model predicted concentrations. As our goal was not to make any direct conclusions from the in vivo data, aside from model verification there was no specific power analysis to be done to calculate a necessary sample size. Unfortunately we were not able to recruit 8 subjects in each of the oral consumption categories as we found the the vast majority of pregnant individuals that we recruited were using THC by inhalation. However, more than 80% of our collected samples were from individuals who used cannabis more than 12 hours before the sample collection. At this time, the drug is fully absorbed and has reached distribution equilibrium in maternal and fetal plasma and fetal tissue. Therefore there should be no difference in the fetal/maternal plasma ratio or fetal tissue/maternal plasma ratio between routes of administration. This enabled us to pool our results from inhalation and oral administration of THC. Due to this we changed our goal to 16 subjects in each trimester with combined inhalation and oral THC use.
Data exclusions	For the T1/T2 termination study, the eligibility criteria were: 1) pregnant person seeking termination who had already consented to a termination procedure via dilation and curettage (D&C) or dilation and evacuation (D&E); 2) 18 years of age or older; 3) able to speak and read English; 4) intrauterine pregnancy confirmed with ultrasound; 5) gestational age 8-24 weeks as determined by ultrasound dating; 6) have used THC-containing cannabis via smoking or oral ingestion within 48 hours of pregnancy termination; 7) have not used other recreational substances (heroin, opiates, benzodiazepines, cocaine, amphetamines/methamphetamines, or other substances of abuse) during pregnancy. For the T3 delivery study, the eligibility criteria were: 1) pregnant person, 18 – 45 years of age; 2) singleton fetus; 3) gestational age >16 weeks as determined by last menstrual period and/or early ultrasound; 4) current reported THC-containing cannabis use; 5) able to speak and read English or Spanish; 6) have not used other recreational drugs (alcohol, cocaine, crack, heroin, hallucinogens, inhalants, methamphetamine, prescription pain relievers, or other drugs of abuse) during pregnancy; 7) not coronavirus disease (COVID) positive at delivery (for study personnel collection purposes during the pandemic). Due to these criteria, one participant was disqualified from the T1/T2 study due to a positive urine toxicology test for recreational drug use.
Replication	To ensure reproducibility of the observed results. Quality control samples were included in the analysis of all plasma and tissue samples. Quality controls samples consisted of blank human plasma and placenta/fetal tissues, spiked with cannabinoids, and were processed identically to unknown samples. All quality control samples were within ± 20% of the expected values.
Randomization	As our study was an observational study, with no intervention, randomization was not relevant.
Blinding	As our study was an observational study, with no intervention, blinding was not relevant.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	As our study was an observational study, not a clinical trial, it was not registered.
Study protocol	The study protocol can be found in the methods section of the paper. Since it was not a trial, it is not in any external database.
Data collection	The first arm of the observational study was a trimester 1 and 2 pregnancy termination study conducted in collaboration with the Birth Defects Research Laboratory at the University of Washington while the second was a trimester 3 pregnancy delivery study

conducted at the University of Colorado. All in vivo samples were collected between January 2021 and May 2023.

Outcomes

The primary outcome of the collected in vivo samples were to quantify umbilical venous plasma and fetal tissue concentrations relative to the respective maternal plasma concentrations for the purpose of verifying the maternal fetal PBPK model. Due to the nature of our in vivo study and the uncertainty of dosing timing/amount we did not have any outcomes from the collected samples that were independent of the PBPK modeling.

Plants

Seed stocks

n/a

Novel plant genotypes

n/a

Authentication

n/a