

Dose Estimation Utility in a Population Pharmacokinetic Analysis of Inhaled Δ9-Tetrahydrocannabinol (THC)

Cannabis Market Products in Occasional and Daily Users

Background

- Desire to understand THC PK in context of high-potency market-derived cannabis product instead of previous studies of low-potency NIDA product.
- Pharmacometric modeling → Precise knowledge of drug dose and timing of samples
- Kinetics of recreational drug PK modeling → Dose is unknown and timing of samples is imprecise
- Purpose: Use pharmacometric study design elements to better estimate dose across cannabis products and type of users

Methods

- 30 subjects stratified to 3 groups daily concentrate (60-90% THC) daily flower (16-30% THC) occasional flower (16-30% THC).
- Because of DEA regulations: subjects supplied their usual product and devices and should inhale cannabis in their usual manner to their usual desired effect.
- FractionTHC (product label) times the difference of weight of the product before and after usage was used to calculate a ‘weighed’ dose
- Only restriction was 15 min time limit and announce their last inhale.
- Blood samples were collected before the first inhalation and 1, 5, 10, 30, 60, 90, and 145 minutes following last inhalation.
- For this analysis baseline THC concentrations were subtracted for all measurements.

Modeling Approach

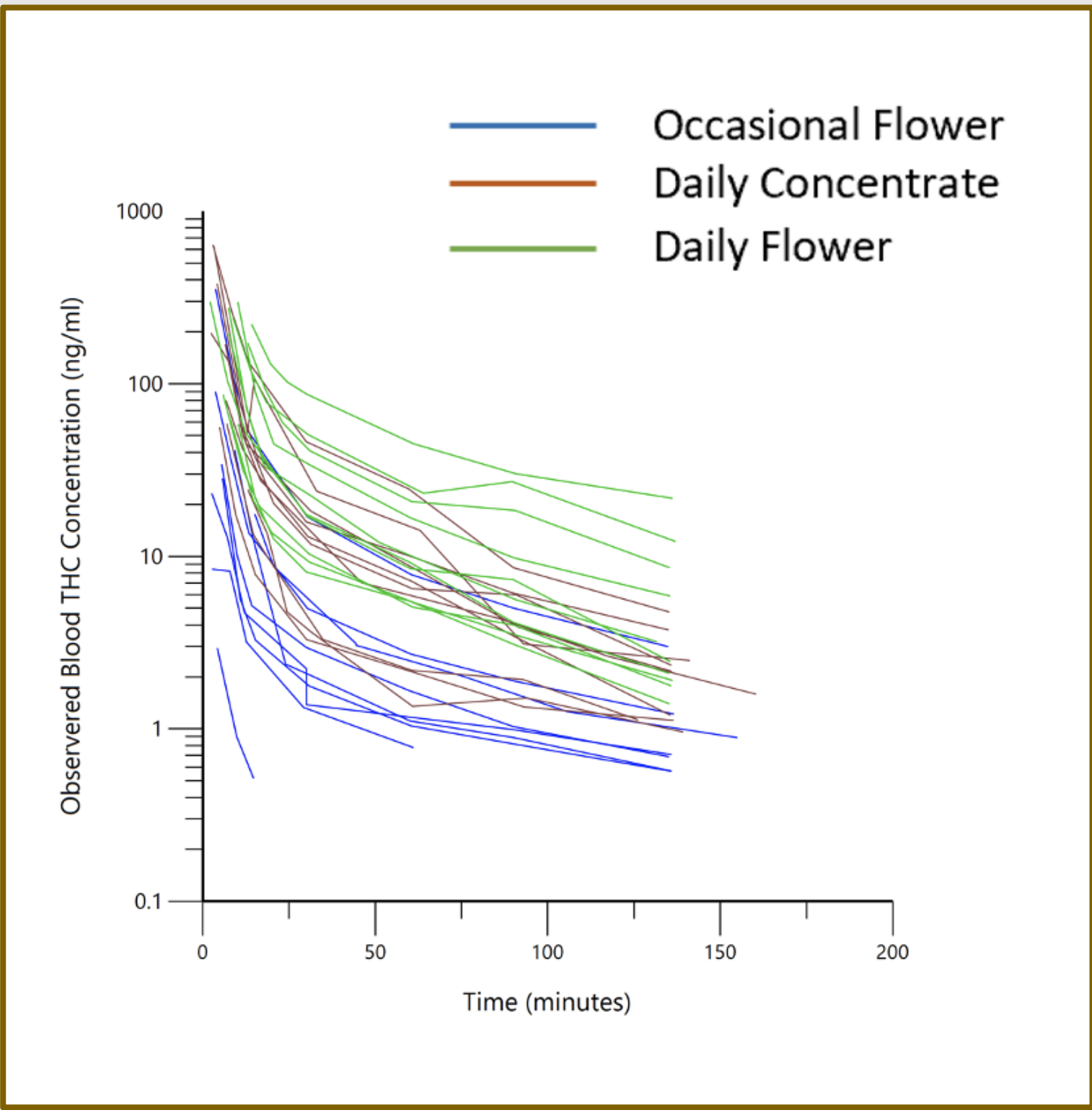


Figure 1. Observed blood THC concentration versus time for all 29 subjects (each line connects the measured concentrations from one subject) after subtraction of the baseline (before inhalation) blood THC concentration. Blue lines are occasional flower users, brown lines are daily concentrate users and green lines are daily flower users.

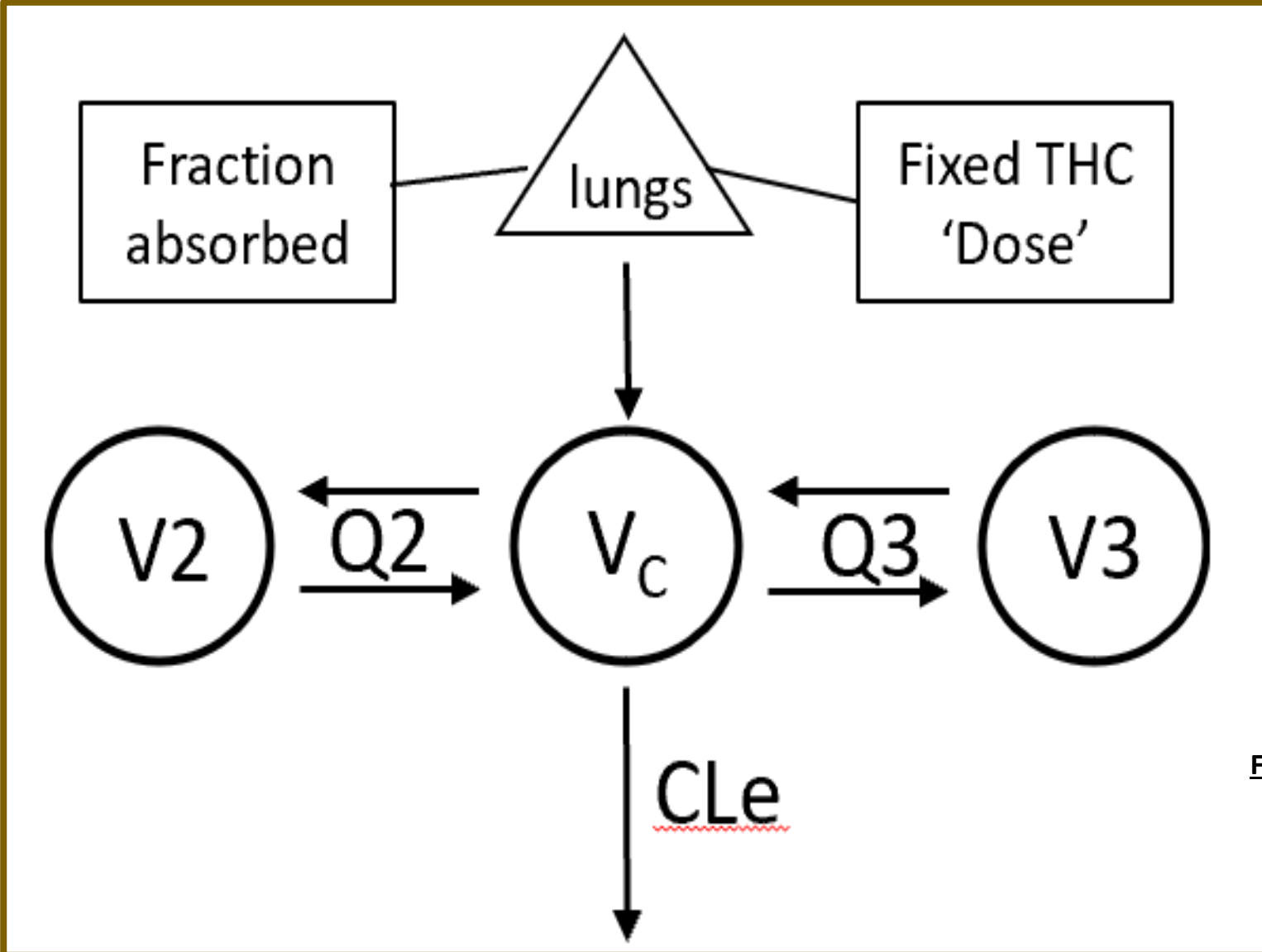


Figure 2. Pharmacokinetic Model

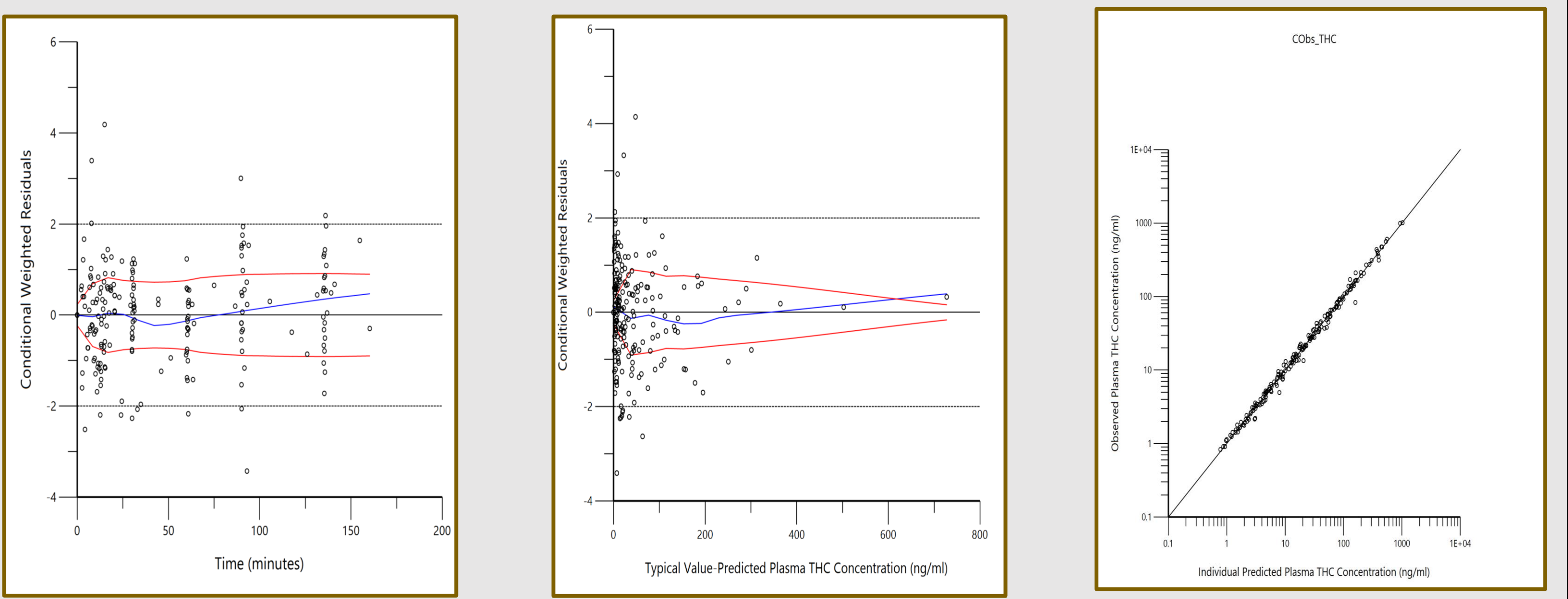


Figure 3a. Conditional weighted residual versus time. Red lines are the locally weighted scatterplot smoothing lines (LOWESS) for the absolute residuals and its mirror. Blue line is the LOWESS line at the 50th percentile.

Figure 3b. Conditional weighted residual versus the population predicted plasma concentrations for THC. Red lines are locally weighted scatterplot smoothing lines (LOWESS) for the absolute residuals and its mirror. Blue line is the LOWESS line at the 50th percentile. Note: Observed plasma THC concentrations are converted from blood THC concentrations (blood/plasma= 0.63).

Figure 3c. Observed versus individual-predicted plasma THC concentrations with inclusion of the covariate. Line of identity represented by the black line. Note: Observed plasma THC concentrations are converted from blood THC concentrations (blood/plasma= 0.62).

	Typical value	±	SEE	ω ²	±	SEE	shrinkage
VC (L)	17.9	±	1.20	0.044	±	0.044	0.29
V2 (L)	51.6	±	4.66	0.16	±	0.16	0.10
V3* (L)	3327						
Q2 (L/min)	1.65	±	0.14	0.13	±	0.046	0.25
Q3 (L/min)	1.75	±	0.10				
Cle* (L/min)	0.72						
FI	0.12	±	0.03	0.82	±	0.02	0.004
covariate _(daily user)	1.79	±	0.29				
δ	0.15	±	0.02				

Table 1. Parameters of the final pharmacokinetic model (*parameters fixed to values from Sempio et al¹¹). Cle = elimination clearance of THC. VC, V2, V3 = volumes of the central, fast and slow equilibrating THC compartments, respectively. Q2 and Q3 = intercompartmental clearances to the fast and slow compartments, respectively. FI = fraction of nominal inhaled (bioavailable) THC ‘dose’ (15mg). Covariate_{daily user} = value of the covariate for the estimated, inhaled THC dose for both concentrate and flower users where default is Covariate_{occasional user} = 0. δ = proportional (relative) intra-subject variability. ω²= inter-subject variability. SEE = standard error of the estimate.

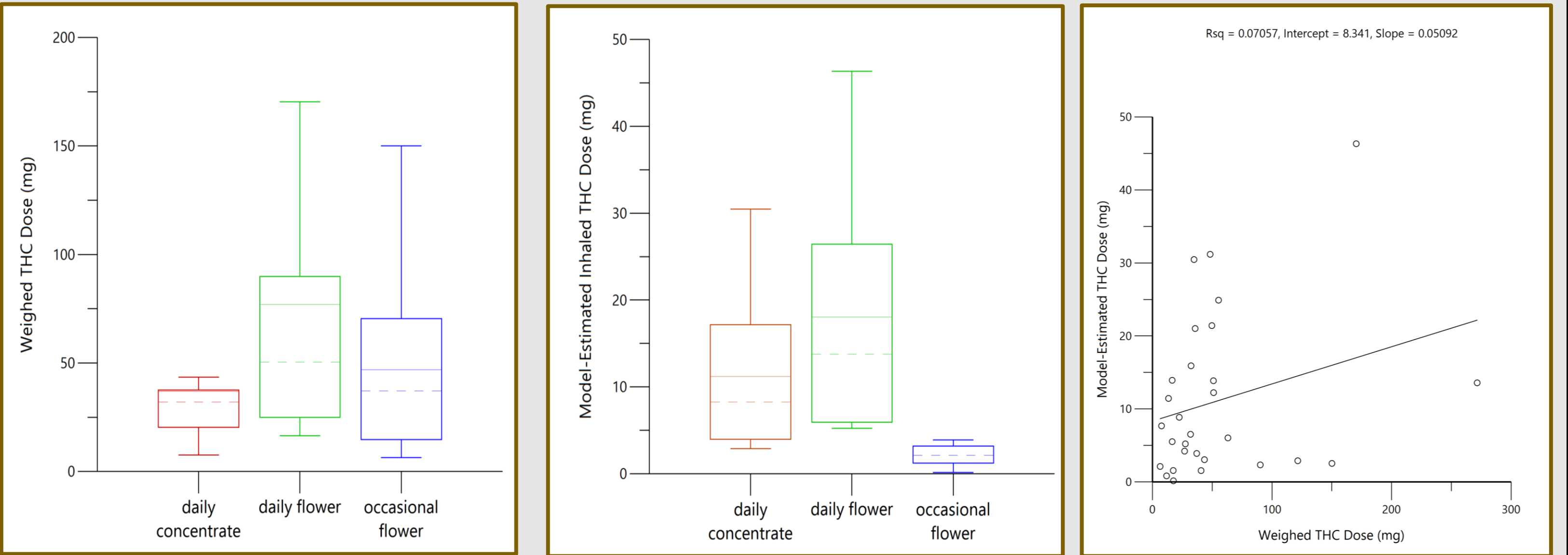


Figure 4a. Box plots of weighed THC doses with colors coded to match Figure 2. The dashed lines are the median; the solid lines are the mean. The ends of the “box” are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile, and the highest value within 1.5 IQR of the upper quartile, where IQR is the interquartile range.

Figure 4b. Box plots of model-estimated inhaled THC doses with colors coded to match Figure 2. The dashed lines are the median; the solid lines are the mean. The ends of the “box” are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile, and the highest value within 1.5 IQR of the upper quartile, where IQR is the interquartile range.

Figure 5. Plot of weighed THC doses and model-estimated inhaled THC doses for all subjects. Circles represent the values for each individual and the black line is the linear regression through the origin.

Conclusion

- Population pharmacokinetic analysis of blood THC versus time data for 2.25 hours following *ad libitum* inhaled consumption of market cannabis flower and high concentrate products fits extremely well within the framework of previous THC pharmacokinetic modeling and descriptive data.
- The pharmacokinetics of THC does not vary with the potency of the inhaled cannabis product.
- Blood THC concentrations provide a more relevant and accurate estimate of THC dose than that obtained through measurement of the mass of cannabis product combusted

Acknowledgments

- This work was supported by the National Institutes of Health (R01 DA 049800)
- Sempio, C., Huestis, M. A., Mikulich-Gilbertson, S. K., Klawitter, J., Christians, U., & Henthorn, T. K. (2020). Population pharmacokinetic modeling of plasma Delta9-tetrahydrocannabinol and an active and inactive metabolite following controlled smoked cannabis administration. Br J Clin Pharmacol, 86(3), 611-619.