

SUPPLEMENTARY MATERIALS

Predicting Δ -9-tetrahydrocannabinol-Induced Psychoactive and Cognitive Effects: A PBPK-PD Approach to Quantifying Feeling High and Reduced Alertness

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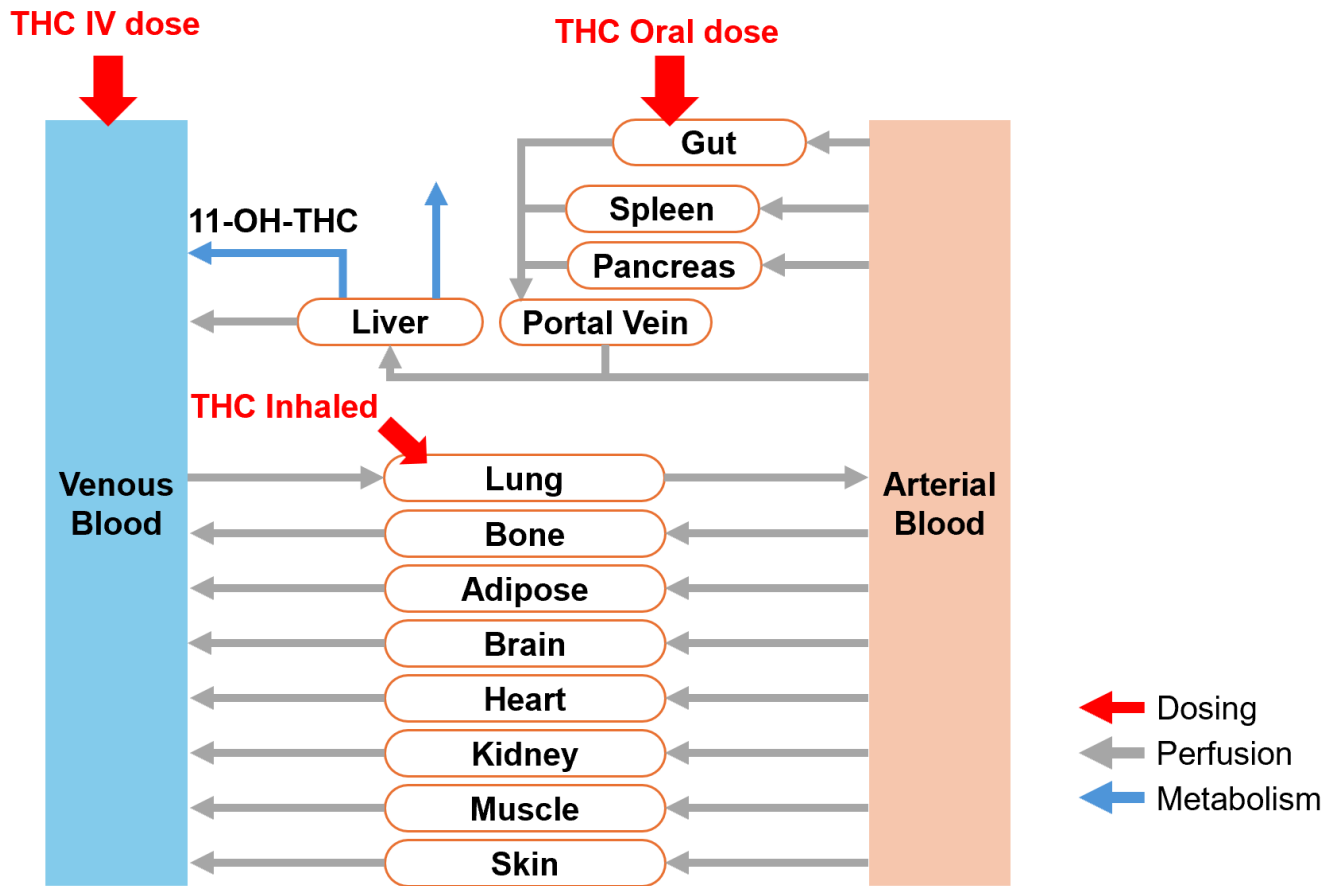


Figure S1. Schematic diagram of the organ compartments used in the whole-body physiologically based pharmacokinetic model for Δ -9-tetrahydrocannabinol (THC) and 11-hydroxy-THC (11-OH-THC). 11-OH-THC is metabolized from THC in the liver and then enters the systemic circulation. IV, intravenous.

Table S1. PBPK-PD predicted and observed VAS “feeling high” and VAS “alertness” scores following delta-9-tetrahydrocannabinol (THC) administration in healthy adults.

Formulation	Trial	PD Group ^a	PK Group ^b	Dose regimen	Absorption Parameters	Observed R _{max} (mm)	Predicted R _{max} (mm)	R _{max} Predicted: Observed
VAS “feeling high”								
IV	D'Souza 2004 ¹	Modeling	/	2.5 mg	/	52.1	52.6	1.01
		Modeling	/	5 mg	/	41.5	59.6	1.44
Oral	Wachtel 2000 ²	Verification	/	7.5 mg	f _a = 0.45, k _a = 0.7/h	18.5	9.8	0.53
		Verification	/	15 mg	f _a = 0.45, k _a = 0.7/h	19.9	19.6	0.98
	Bedi 2013 ³	Verification	/	10 mg	f _a = 0.45, k _a = 0.7/h	21.6	13.1	0.61
		Verification	/	20 mg	f _a = 0.45, k _a = 0.7/h	17.3	24.7	1.43
	Schoedel 2018 ⁴	Verification	/	10 mg	f _a = 0.45, k _a = 0.7/h	29.7	13.7	0.46
		Verification	/	30 mg	f _a = 0.45, k _a = 0.7/h	56.3	32.0	0.57
Inhaled	Strougo 2008 ⁵	Modeling	Type 1	2, 4, 6, 8 mg	lung f _a = 0.6, lung k _a = 200/h	1.78 ^c	1.83 ^c	1.03
	Matheson 2020 ⁶	Verification	Type 1	73.3 mg ^d	lung f _a = 0.025, lung k _a = 12/h	60.5	42.2	0.70
		Verification	Type 1	86 mg ^e	lung f _a = 0.05, lung k _a = 12/h	65.5	52.9	0.81
	Penetar 2005 ⁷	Verification	Type 2	16.5 mg ^d	lung f _a = 0.22, lung k _a = 200/h	51.3	49.9	0.97
		Verification	Type 2	16.5 mg ^e	lung f _a = 0.4, lung k _a = 200/h	69.3	62.9	0.91
		Verification	Type 2	29.8 mg ^d	lung f _a = 0.22, lung k _a = 200/h	66.5	62.9	0.95
	Klumpers 2012 ⁸	Verification	Type 2	29.8 mg ^e	lung f _a = 0.4, lung k _a = 200/h	80.1	71.4	0.89
		Verification	Type 2	2, 6, 6 mg	lung f _a = 0.6, lung k _a = 200/h	1.52 ^c	1.76 ^c	1.16
VAS “alertness”								
Inhaled	Strougo 2008 ⁵	Modeling	Type 1	2, 4, 6, 8 mg	lung f _a = 0.6, lung k _a = 200/h	35.3	36.4	1.03
	Hunault 2014 ⁹	Verification	Type 1	29.3 mg	lung f _a = 0.22, lung k _a = 12/h	47.9	39.6	0.83
		Verification	Type 1	49.1 mg	lung f _a = 0.22, lung k _a = 12/h	46.7	37.3	0.80
		Verification	Type 1	69.4 mg	lung f _a = 0.22, lung k _a = 12/h	30.8	29.5	0.96
	Dumont 2011 ¹⁰	Verification	Type 2	4, 6, 6 mg	lung f _a = 0.6, lung k _a = 200/h	42.0	45.1	1.07
	Mokrysz 2016 ¹¹	Verification	Type 2	8 mg	lung f _a = 0.9, lung k _a = 200/h	39.5	46.7	1.18

R_{max}, mean peak VAS “feeling high” score or mean trough VAS “alertness” score; IV, intravenous; /, not applied; f_a, fraction of oral absorption; k_a, first-order oral absorption rate constant; lung f_a, fraction of drug absorbed from the lung; lung k_a, first-order absorption rate constant of lung absorption.

^a Modeling: dataset was used for developing the PD model; Verification: dataset was used for PD model verification.

^b Type 1: clinical trials with THC concentration-time profiles included in our previous THC PBPK study and PBPK-PD study^{12, 13}; Type 2: clinical trials provided only dosing information but no THC concentration-time profiles.

^c The Log₁₀(VAS + 2) was reported in the original studies.

^d female subjects only.

^e male subjects only.

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