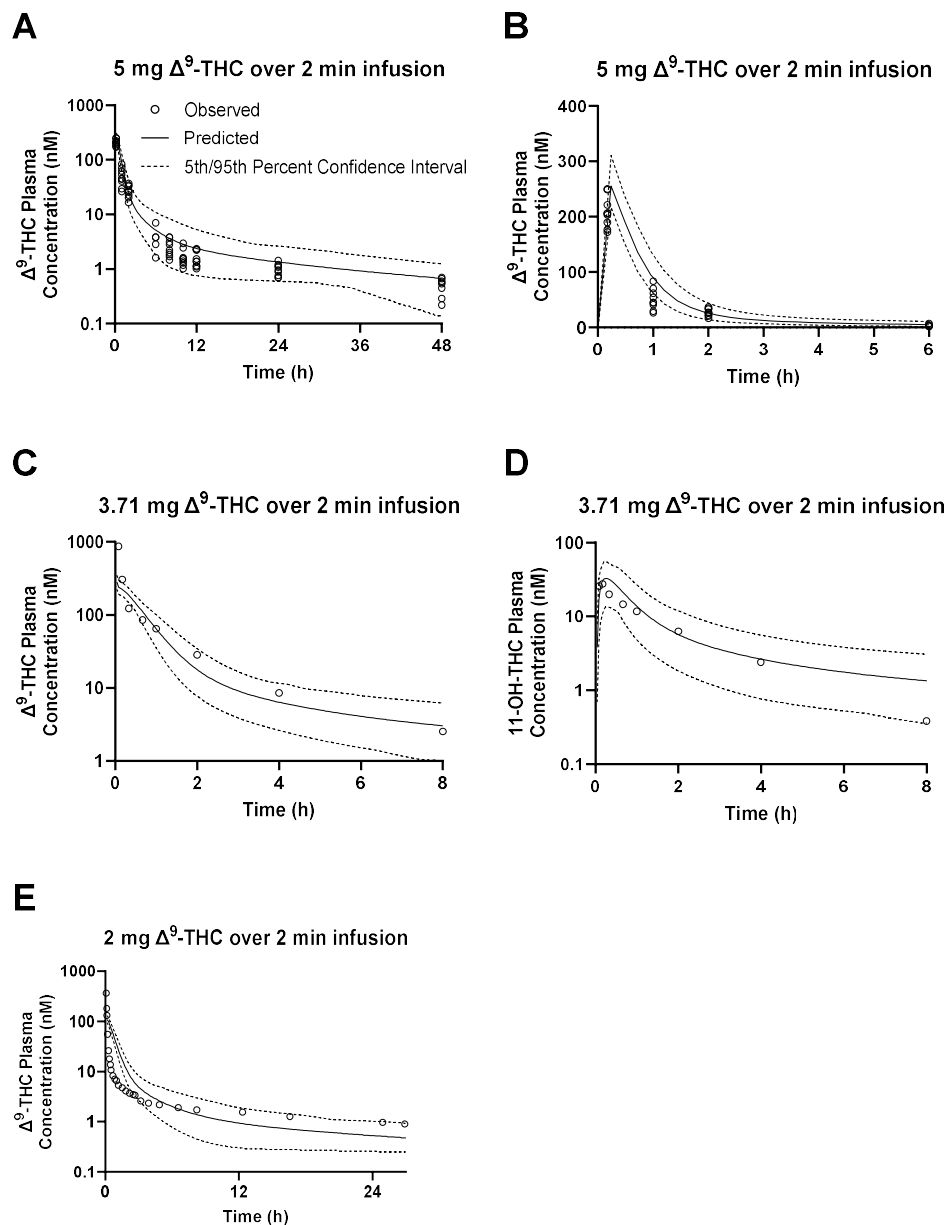
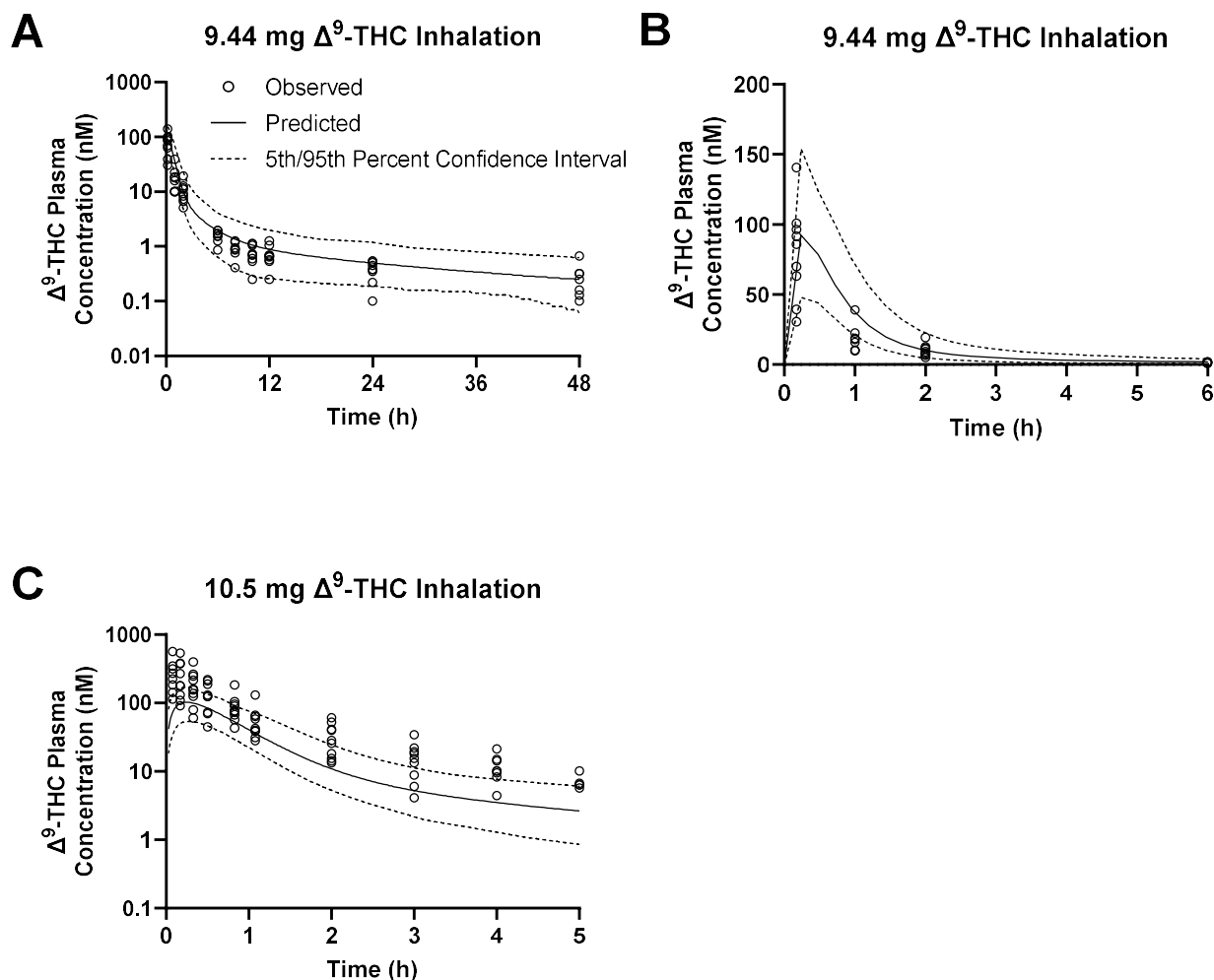


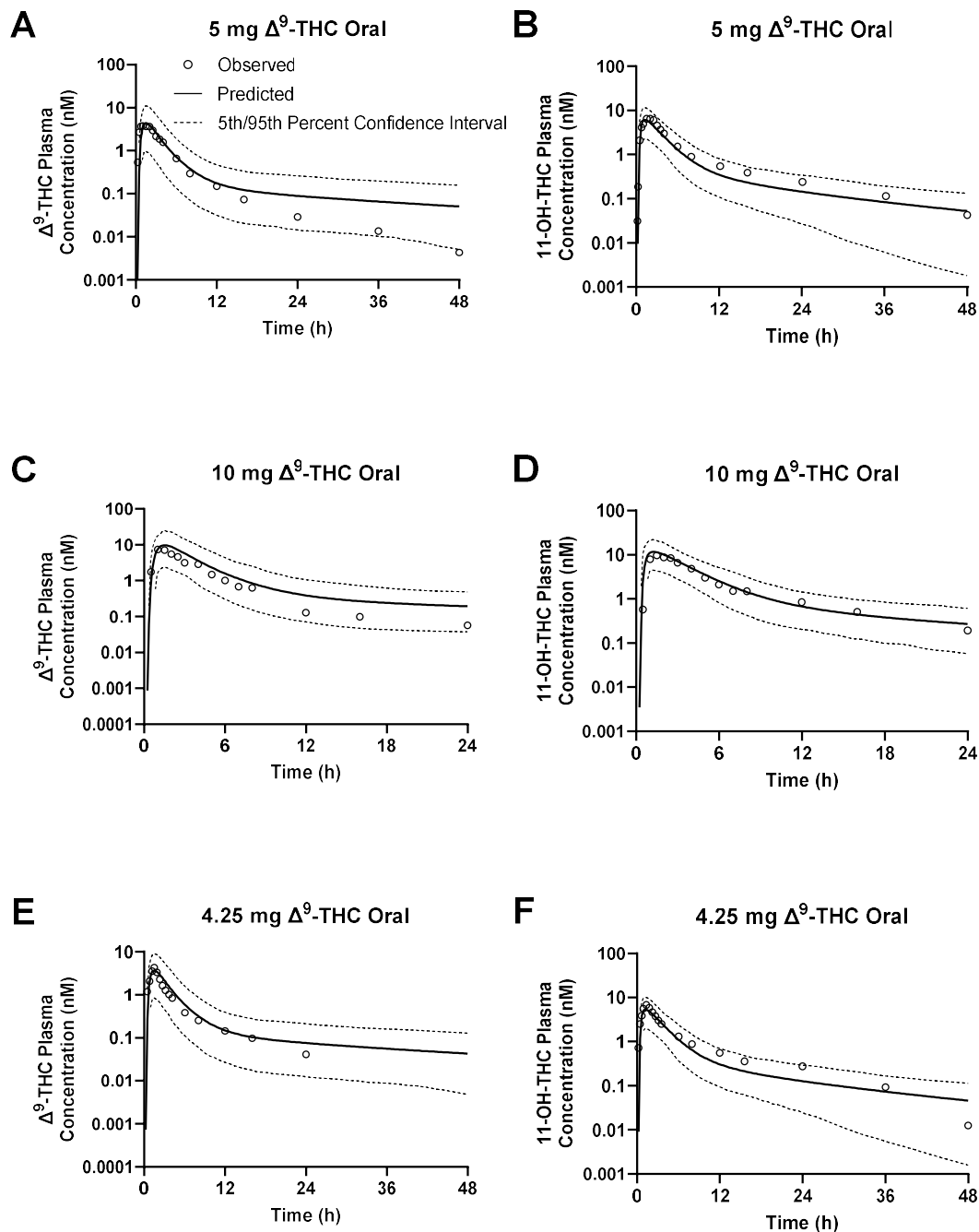
SUPPLEMENTARY INFORMATION



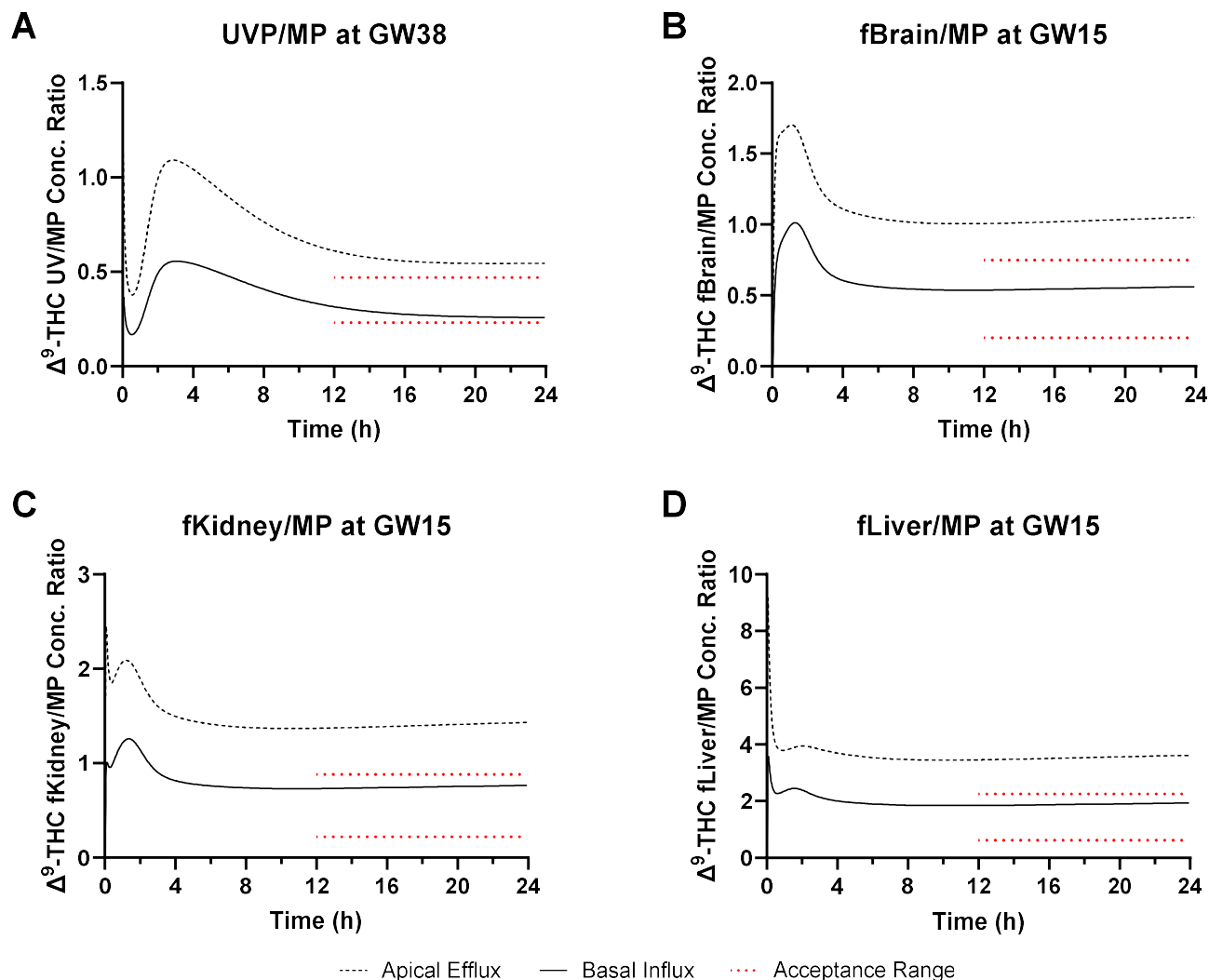
Supplementary Figure 1: Non-pregnant observed and PBPK model predicted Δ^9 -THC and 11-OH-THC plasma concentration-time profiles after intravenous Δ^9 -THC administration to healthy volunteers. (A, B) The Δ^9 -THC systemic disposition parameters were optimized using this training dataset¹. Panel B shows the data in panel A truncated to 6 hours. (C – E) Then, without changing the values of these parameters, the model was verified with these two independent datasets^{2,3}. 11-OH-THC plasma concentrations, after Δ^9 -THC administration, were measured in only the Naef 2004 study³. All predicted/observed Δ^9 -THC ratios for AUC_{inf} ($AUC_{inf}R$) and C_{max} ($C_{max}R$) fell within the acceptance range, i.e., 0.67-1.43 and 0.44-1.47, respectively. Data (individual or mean) were digitized using the WebPlotDigitizer, version 4.6.



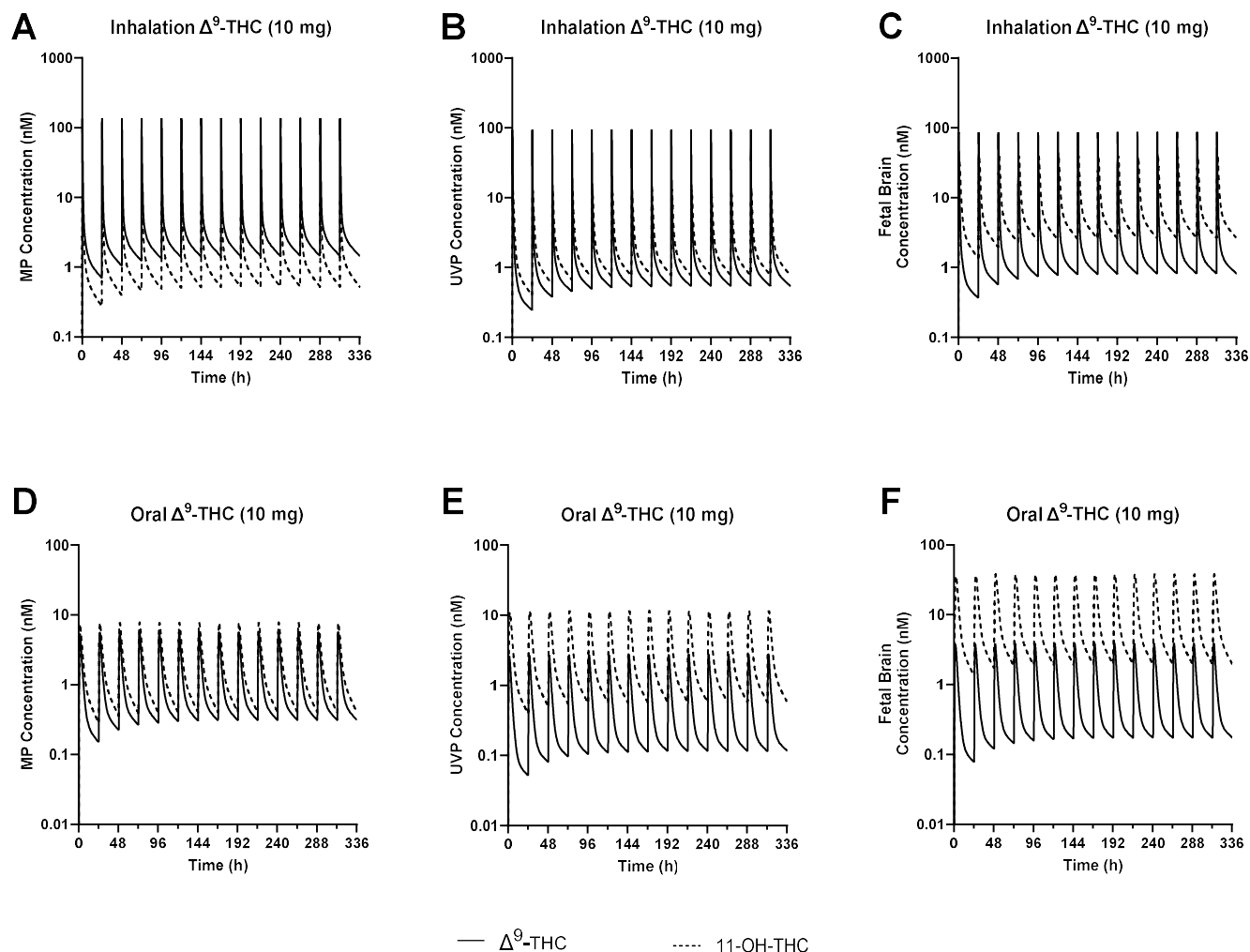
Supplementary Figure 2: Non-pregnant observed and PBPK model predicted Δ^9 -THC plasma concentration-time profiles after inhalation Δ^9 -THC administration to healthy volunteers. (A, B) The Δ^9 -THC inhalation absorption kinetics were optimized using this training dataset¹. Panel B shows the data in panel A truncated to 6 hours. (C) Then, without changing the Δ^9 -THC absorption parameters, the model was verified with this independent dataset⁴. All predicted/observed AUC_{inf}R and C_{max}R fell within the acceptance range, 0.45-1.27 and 0.55-1.10, respectively. 11-OH-THC plasma concentrations were not measured in these studies. Data (individual or mean) were digitized using the WebPlotDigitizer, version 4.6.



Supplementary Figure 3: Non-pregnant observed and PBPK model predicted Δ^9 -THC and 11-OH-THC plasma concentration-time profiles after oral Δ^9 -THC administration to healthy volunteers. (A, B) The Δ^9 -THC oral absorption kinetics and 11-OH-THC systemic disposition parameters were optimized using this training dataset⁵. (C-F) Then, without changing these parameters, the model was verified with these two independent datasets^{6,7}. All predicted/observed AUC_{inf}R and C_{max}R fell within the acceptance range, 0.73-1.48 and 0.69-1.41, respectively. Data (individual or mean) were digitized using the WebPlotDigitizer, version 4.6.



Supplementary Figure 4: m-f-PBPK model predicted steady-state profiles of Δ^9 -THC umbilical venous plasma/maternal plasma (UVP/MP) at GW 38 as well as fetal tissue/MP (fTissue/MP) at GW 15 after daily maternal Δ^9 -THC inhalation (100 mg; 318 μ mol). The m-f-PBPK model predicted profiles were generated with either Δ^9 -THC basal influx transport (solid line) or apical efflux transport (dashed line) at the basal and apical membrane of the syncytiotrophoblast, respectively. Only Δ^9 -THC basal influx transport predicted trimester 3 (GW38) UVP/MP (A) and trimester 2 (GW15) fetal brain/MP (B), fetal kidney/MP (C), and fetal liver/MP (D) values within the acceptance criteria (red dotted lines) as computed from the *in vivo* observed data. Note, these profiles are independent of the consumed dose and route of administration. The *in vivo* observed data were collected when distribution equilibrium between plasma and tissue Δ^9 -THC concentrations was expected to have been reached (i.e. >12 hours). To compare with the observed data, the predicted GW15 fetal tissue concentrations included the Δ^9 -THC concentration in the blood within the tissues (see methods).



Supplementary Figure 5: M-f-PBPK model predicted Δ^9 -THC and 11-OH-THC steady-state plasma concentrations in the MP, UVP and fetal brain after daily consumption of Δ^9 -THC (10 mg (32 μ mol) inhalation or 10 mg (32 μ mol) oral) at gestational week 15. At steady-state, there was marginal accumulation in the plasma of both Δ^9 -THC and 11-OH-THC (<1.1) irrespective of the route of administration. In addition, as expected, the AUC_{ss} and $C_{ss,avg}$ of 11-OH-THC after oral Δ^9 -THC consumption was greater than that after inhalation. Consistent with human adult postmortem data, 11-OH-THC fetal brain/UVP concentrations were predicted to be higher than those for Δ^9 -THC. Δ^9 -THC: 1 nM = 0.314 ng/mL; 11-OH-THC: 1 nM = 0.330 ng/mL.

Supplementary Table 1: Drug and System-Dependent Input Parameters for the Non-pregnant and the Maternal-Fetal PBPK Models

Parameter	Δ^9 -THC	11-OH-THC	Reference
Physiochemical and Binding			
Molecular Weight (g/mol)	314.15	330.46	ChEMBL
Log P	6.97	6.31	⁸
Ionization Type	Neutral	Neutral	ChEMBL
B/P	0.667	0.625	⁹
$f_{u,p}$	0.011	0.012	¹⁰
Absorption			
Oral f_a	0.38	N/A	⁵
Oral k_a (1/h)	0.60	N/A	Optimized with ⁵
$f_{u,gut}$	0.38	N/A	Optimized with ⁵
Q_{gut} (L/h)	16.9	N/A	Simcyp Predicted
Inhalation f_a	0.21	N/A	¹
Inhalation k_a (1/h)	10.4	N/A	Optimized with ¹
Inhalation F	0.208	N/A	⁸
Distribution			
$K_{p,liver}$	51.0	6.51	Optimized with ¹¹⁻¹³
$K_{p,kidney}$	2.04	1.47	Optimized with ¹¹⁻¹³
$K_{p,brain}$	1.50	3.53	Optimized Δ^9 -THC with ¹²⁻¹⁵ ; 11-OH-THC with ^{12,13}
$K_{p,muscle}$	0.063	0.001	Optimized with ¹
$K_{p,adipose}$	23.1	Remaining tissue	Optimized with ¹
$K_{p,skin}$	1.59	Remaining tissue	Optimized with ¹
$K_{p,tissue}$ (remaining tissues)	Various	Various	Predicted via Rodgers and Rowland (Simcyp Method 2)
Elimination			
CYP2C9 V_{max} (pmol/min/mg protein)	17.0	N/A	Estimated from ¹ and ¹⁰ with a middle-out approach
CYP2C9 K_m (nM)	2.91	N/A	¹⁰
CYP3A CL_{int} (μL/min/mg protein)	578	N/A	Estimated from Δ^9 -THC from ¹ and ¹⁰
Total Hepatic CL_{int} (μL/min/mg protein)	N/A	3763	Estimated from ⁵ using a middle-out approach
Pregnancy			
$f_{u,p,fetus}$	0.0071	0.0067	Measured by us
$CL_{int, fh}$ (L/h)	GW15: 23.0 GW25: 153 GW38: 519 GW40: 595	GW15: 3.37 GW25: 22.4 GW38: 76.1 GW40: 87.2	Estimated from ¹⁶
$CL_{int, PD}$ (L/h)	GW15: 43.9 GW25: 110 GW38: 226 GW40: 247	GW15: 35.4 GW25: 88.4 GW38: 182 GW40: 199	Estimated from ¹⁷
$CL_{int, T}$ (L/h)	GW15: 74.8 GW25: 187 GW38: 385 GW40: 420	N/A	Estimated from ¹⁷
Assuming Influx at the Basal Membrane of the Syncytiotrophoblast			

N/A: not applicable; GW: gestational week; LogP: octanol-water partition coefficient; B/P: blood to plasma ratio; $f_{u,p}$: fraction unbound in the adult non-pregnant plasma; f_a : fraction absorbed; k_a : rate of absorption; F: bioavailability; $f_{u,gut}$: fraction unbound in the gut; Q_{gut} : blood flow in the gut; K_p : tissue to plasma ratio; CYP: cytochrome P450; V_{max} : maximum rate of metabolism; K_m : Michaelis-Menten constant; CL_{int} : intrinsic clearance; $f_{u,p,fetus}$: fraction unbound in the fetal plasma; $CL_{int, fh}$: intrinsic fetal hepatic clearance; $CL_{int, PD}$: intrinsic placental passive diffusion; $CL_{int, T}$: intrinsic placental transport.

Supplementary Table 2: Demographics of the Subjects who Completed the T1/T2 or the T3 Study

		Trimester 1 n = 18	Trimester 2 n = 22	Trimester 3 n = 26
Maternal Race	White	10 (56%)	17 (77%)	11 (42%)
	Black	2 (11%)	3 (14%)	12 (46%)
	Native American	1 (5.6%)	0 (0%)	0 (0%)
	Asian or Pacific Islander	2 (11%)	2 (9.1%)	1 (3.8%)
	Hispanic	0 (0%)	0 (0%)	1 (3.8%)
	Other/ Mixed	3 (17%)	0 (0%)	1 (3.8%)
Gestational age at delivery (days)		71 ± 8.0	105 ± 14	267 ± 12
Fetal Sex* (male ♂; female ♀)		7 (35%) ♂ 13 (65%) ♀	16 (73%) ♂ 6 (27%) ♀	Not Collected
Maternal age (years)		29 ± 5.3	26 ± 5.3	26 ± 5.2
Tobacco use within one month of sample collection**		10 (56%)	9 (41%)	7 (27%)
*One T1 subject had triplets and one T2 subject's fetal sex could not be ascertained; **Self-reported Data are either n (%) or mean ± SD				

Supplementary Table 3: Observed Δ^9 -THC, 11-OH-THC, and COOH-THC Concentrations in Maternal Plasma, Umbilical Venous Plasma, and Placenta Tissues in Trimester 3 after Oral or Inhalation Consumption of Cannabis

	Inhalation Consumption	Oral Consumption	MP (nM)	UVP (nM)	UVP/MP	Placenta Mean (nM)	Placenta/ MP	MP (nM)	UVP (nM)	UVP/MP	Placenta Mean (nM)	Placenta/ MP	MP (nM)	UVP (nM)	UVP/MP	Placenta Mean (nM)	Placenta/ MP
	Δ^9 -THC						11-OH-THC						COOH-THC				
1	---; > 72 hours	---, ---	BLOQ	BLOQ	---	---	---	BLOQ	BLOQ	---	BLOQ	---	BLOQ	BLOQ	---	BLOQ	---
2	0.75 grams; > 72 hours	---, ---	BLOQ	BLOQ	---	---	---	BLOQ	BLOQ	---	BLOQ	---	BLOQ	BLOQ	---	BLOQ	---
4	0.25 grams; 12-24 hours	---, ---	46	14	0.31	9.2	0.20	26	5.2	0.20	27	1.04	1304	163	0.13	109	0.084
5	0.0625 grams; 12-24 hours	100 mg; > 72 hours	3.8	1.0	0.28	1.2	0.32	BLOQ	BLOQ	---	BLOQ	---	12	5.40	0.45	6.0	0.50
6	0.0625 grams; 24-36 hours	---, ---	7.1	1.7	0.24	2.0	0.28	1.1	BLOQ	---	BLOQ	---	54	18	0.34	9.7	0.18
7	0.125 grams; > 72 hours	10-20 mg; > 72 hours	0.98	0.13	0.14	0.21	0.21	0.62	BLOQ	---	BLOQ	---	6.90	2.90	0.42	2.8	0.41
8	---; > 72 hours	---, ---	5.7	2.5	0.44	1.4	0.24	BLOQ	BLOQ	---	BLOQ	---	52	18	0.35	9.4	0.18
9	0.75 grams; > 72 hours	---, ---	BLOQ	BLOQ	---	---	---	BLOQ	BLOQ	---	BLOQ	---	BLOQ	BLOQ	---	BLOQ	---
10	---; 24-36 hours	---, ---	17	4.2	0.25	4.9	0.29	BLOQ	BLOQ	---	BLOQ	---	108	41	0.38	25	0.23
13	0.5 grams; 24-36 hours	50 mg; > 72 hours	5.9	---	---	0.78	0.13	3.1	---	---	BLOQ	---	33	---	---	4.2	0.13
15	3.5 grams; 36-48 hours	7 mg; 48-72 hours	11	3.9	0.34	5.2	0.46	3.0	BLOQ	---	BLOQ	---	190	40	0.21	---	---
18	0.75 grams; 36-48 hours	---, ---	3.6	1.8	0.50	1.6	0.44	BLOQ	BLOQ	---	BLOQ	---	21	9.0	0.44	BLOQ	---
19	0.25 grams; > 72 hours	---, ---	4.5	1.2	0.27	2.5	0.56	BLOQ	BLOQ	---	BLOQ	---	99	19	0.19	13	0.13
20	0.25 grams; > 72 hours	---, ---	7.7	2.4	0.31	3.1	0.40	0.93	BLOQ	---	BLOQ	---	76	8.2	0.11	BLOQ	---
21	1 gram; 24-36 hours	---, ---	3.2	1.3	0.40	1.6	0.50	0.86	BLOQ	---	BLOQ	---	19	4.3	0.23	9.0	0.48
22	1 gram; 12-24 hours	---, ---	1.9	0.41	0.22	1.2	0.64	BLOQ	BLOQ	---	BLOQ	---	17	5.1	0.30	BLOQ	---
23	0.125 grams; 24-36 hours	---, ---	5.3	1.9	0.35	1.1	0.21	0.85	BLOQ	---	BLOQ	---	16	6.6	0.42	BLOQ	---
24	0.5 grams; 24-36 hours	5 mg; 48-72 hours	BLOQ	BLOQ	---	0.38	---	BLOQ	BLOQ	---	BLOQ	---	0.98	BLOQ	---	BLOQ	---
25	---; 48-72 hours	---, ---	6.3	1.7	0.27	1.6	0.25	BLOQ	BLOQ	---	BLOQ	---	82	38	0.47	24	0.29
27	---; ---	10 mg; > 72 hours	BLOQ	BLOQ	---	2.3	---	BLOQ	BLOQ	---	BLOQ	---	BLOQ	BLOQ	---	BLOQ	---
28	1 gram; 4-12 hours	---, ---	0.90	0.62	0.69	---	---	BLOQ	BLOQ	---	BLOQ	---	9.60	4.6	0.48	BLOQ	---
29	0.3 grams; 12-24 hours	---, ---	0.45	BLOQ	---	---	---	BLOQ	BLOQ	---	BLOQ	---	1.60	0.92	0.58	BLOQ	---
30	3.5 grams; >72 hours	---, ---	6.7	2.2	0.33	---	---	BLOQ	BLOQ	---	BLOQ	---	25	5.4	0.22	BLOQ	---
32	0.125 grams; 24-36 hours	---; 24-36 hours	3.3	1.5	0.44	---	---	BLOQ	BLOQ	---	BLOQ	---	39	9.1	0.23	BLOQ	---
33	2 vape hits; 48-72 hours	10 mg; >72 hours	18	BLOQ	---	---	---	9.4	BLOQ	---	BLOQ	---	150	BLOQ	---	BLOQ	---
34	1 gram; 24-36 hours	---, ---	6.5	3.2	0.49	4.9	0.76	2.2	BLOQ	---	BLOQ	---	53	45	0.85	BLOQ	---
Mean $\pm$ SD (%CV)				0.35 $\pm$ 0.13 (37)		0.37 $\pm$ 0.18 (48)		0.20			1.04		0.36 $\pm$ 0.18 (49)			0.26 $\pm$ 0.15 (58)	

BLOQ: below limit of quantification; ---: no sample/data collected and/or ratio cannot be calculated; Self-reported dosing information is listed for last consumption of Δ^9 -THC (amount; time since last consumption) prior to delivery; MP: maternal plasma; UVP: umbilical venous plasma; Δ^9 -THC molecular weight = 314.45 g/mol.

Supplementary Table 4: Observed Δ^9 -THC Concentrations in Maternal Plasma, Placenta, and Fetal Tissue in Trimester 1 and 2 after Oral or Inhalation Consumption of Cannabis

Subject	Gestational Age (days)	Dosing	MP (nM)	Fetal Brain (nM)	Fetal Brain/MP	Fetal Kidney (nM)	Fetal Kidney/MP	Fetal Liver (nM)	Fetal Liver/MP	Placenta Mean (nM)	Placenta/MP
Trimester 1											
H28680	67	---; 4-12 hours	3.4							0.89	0.26
H28688	52	1 gram; < 4 hours	19							36	1.9
H28761	72	3.5 grams; < 4 hours	34							6.9	0.21
H28869	59	80 mg Δ^9 -THC; < 4 hours	24							25	1.0
H28928	67	3 grams; 36-48 hours	26	18	0.68			20	0.75	19	0.71
H28960	78	0.25 grams; 4-12 hours	16							5.4	0.34
H28972	72	0.5 grams; 12-24 hours	7.0							BLOQ	
H28986	78	1 dab/0.25 grams; 12-24 hours	20							13	0.62
H28987	74	1 joint; 12-24 hours	0.56							BLOQ	
H29026	80	1 gram; 4-12 hours	0.52							BLOQ	
H29045	74	0.1 grams; 4-12 hours	2.5							BLOQ	
H29110	82	2 grams; 36-48 hours	20	6.7	0.33					9.9	0.49
H29122	~77	0.5 grams; < 4 hours	37							22	0.60
H29141	67	1 gram; 12-24 hours	3.5							BLOQ	
H90004	74	1 gram; 12-24 hours	3.1							14	4.4
H90006	59	100 mg Δ^9 -THC oral; 12-24 hours	3.6							BLOQ	
H90015	76	2 grams; 12-24 hours	45							12	0.26
H90020	74	100 mg Δ^9 -THC; 4-12 hours	5.0							3.8	0.77
Pool 1			27	13	0.48						
Pool 2			12			11	0.89				
	Range 52 – 82			Mean $\pm$ SD (%CV)	0.50 $\pm$ 0.18 (35)					Mean $\pm$ SD (%CV)	0.96 $\pm$ 1.2 (122)
Trimester 2											
H28718	89	1 gram; 4-12 hours	13							6.2	0.49
H28786	105	1 gram; 12-24 hours	6.4	3.3	0.52	4.0	0.62	11	1.8	4.0	0.62
H28820	94	1 gram; < 4 hours	21							6.2	0.29
H28870	94	0.2 grams; < 4 hours	29							11	0.36
H28894	87	1-2 grams; 4-12 hours	31	6.8	0.22	8.0	0.26	18	0.59	21	0.69
H28896	115	0.2 grams; < 4 hours	0.85	1.0	1.2					BLOQ	
H28913	91	---; 12-24 hours	6.2							3.9	0.62
H28983	108	2 units; 24-36 hours	14	4.8	0.34	5.8	0.41	21	1.5	10	0.73
H28998	91	1 gram; 12-24 hours	4.0	1.3	0.33					2.9	0.72
H29046	127	<2 grams; 12-24 hours	4.4	BLOQ						BLOQ	
H29069	110	0.5 grams; 24-36 hours	14	3.0	0.22	4.6	0.33	8.3	0.59	BLOQ	
H29075	115	0.5 grams; 12-24 hours	0.59	BLOQ						BLOQ	
H29128	94	1 gram; 24-36 hours	28							BLOQ	
H90000	103	1 gram; 4-12 hours	30	10	0.35	9.4	0.32	38	1.3	9.0	0.31
H90003	122	1 gram; < 4 hours	14	8.3	0.59	8.2	0.59	19	1.4	4.5	0.32
H90005	113	---; < 4 hours	5.7	1.8	0.31			4.3	0.75	2.5	0.44
H90010	137	3 mg Δ^9 -THC; 12-24 hours	13	11	0.85	12	0.97	39	3.0	15	1.2
H90012	85	0.2 mg Δ^9 -THC; < 4 hours	8.7							12	1.3
H90014	105	---; 12-24 hours	2.8	1.2	0.41					BLOQ	
H90016	101	---; 12-24 hours	6.3	2.7	0.42			7.3	1.2	3.8	0.60
H90018	103	0.5 mg Δ^9 -THC oil; 4-12 hours	51	12	0.24	17	0.33	94	1.8	30	0.58
H90022	110	3 grams; 12-24 hours	8.6	2.2	0.26			6.5	0.76	4.5	0.53
	Range 85 – 137			Mean $\pm$ SD (%CV)	0.45 $\pm$ 0.28 (63)	Mean $\pm$ SD (%CV)	0.48 $\pm$ 0.24 (50)	Mean $\pm$ SD (%CV)	1.33 $\pm$ 0.71 (54)	Mean $\pm$ SD (%CV)	0.61 $\pm$ 0.29 (47)

BLOQ: below limit of quantification; Blank rows: no sample collected and/or ratio cannot be calculated; Unless otherwise indicated, dosing information is for last consumption of Δ^9 -THC by inhalation prior to termination (amount; time since last consumption); MP: maternal plasma; Δ^9 -THC molecular weight = 314.45 g/mol. Pool 1: 25.7% H28761, 54.7% H28986, 19.6% H90015. Pool 2: 15.2% H28761, 52.0% H28986, 32.8% H90015.

Supplementary Table 5: Observed 11-OH-THC Concentrations in Maternal Plasma, Placenta, and Fetal Tissue in Trimester 1 and 2 after Oral or Inhalation Consumption of Cannabis

Subject	MP (nM)	Fetal Brain (nM)	Fetal Brain/MP	Fetal Kidney (nM)	Fetal Kidney/MP	Fetal Liver (nM)	Fetal Liver/MP	Placenta Mean (nM)	Placenta/MP
Trimester 1									
H28680	BLOQ							BLOQ	
H28688	5.4							5.4	1.0
H28761	7.2								
H28869	6.1							BLOQ	
H28928	9.1	BLOQ				BLOQ		BLOQ	
H28960	4.2							BLOQ	
H28972	1.3							BLOQ	
H28986	5.5							BLOQ	
H28987	BLOQ							BLOQ	
H29026	0.71							BLOQ	
H29045	BLOQ							BLOQ	
H29110	9.8	BLOQ						BLOQ	
H29122	10							BLOQ	
H29141	BLOQ							BLOQ	
H90004	1.7							BLOQ	
H90006	2.2							BLOQ	
H90015	16							5.0	0.31
H90020	BLOQ							BLOQ	
Pool 1	8.0	BLOQ							
Pool 2	3.8			5.2	1.4				
Mean ± SD (%CV)									
Trimester 2									
H28718	3.6							BLOQ	
H28786	BLOQ	BLOQ		BLOQ		BLOQ		BLOQ	
H28820	4.8							BLOQ	
H28870	8.3							BLOQ	
H28894	8.4	BLOQ		3.9	0.46	BLOQ		BLOQ	
H28896	BLOQ	BLOQ		BLOQ		BLOQ		BLOQ	
H28913	2.6							BLOQ	
H28983	6.1	BLOQ		BLOQ		9.2	1.5	BLOQ	
H28998	2.3	BLOQ						BLOQ	
H29046	BLOQ	BLOQ						BLOQ	
H29069	BLOQ	BLOQ		BLOQ		5.1		BLOQ	
H29075	BLOQ	BLOQ						BLOQ	
H29128	10							BLOQ	
H90000	14	BLOQ		6.6	0.46	13	0.91	BLOQ	
H90003	9.3	BLOQ		4.1	0.44	7.7	0.82	BLOQ	
H90005	2.7	BLOQ		BLOQ		BLOQ		BLOQ	
H90010	3.5	BLOQ		6.5	1.8	12	3.4	BLOQ	
H90012	4.5							BLOQ	
H90014	0.96	BLOQ		BLOQ		BLOQ		BLOQ	
H90016	1.3	BLOQ		BLOQ		BLOQ		BLOQ	
H90018	45	13	0.29	18	0.39	46	1.0	BLOQ	
H90022	4.4	BLOQ		2.2	0.50	5.0	1.1	BLOQ	
Mean ± SD (%CV)					0.68 ± 0.56 (83)		1.5 ± 0.99 (67)		

BLOQ: below limit of quantification; Blank rows: no sample collected and/or ratio cannot be calculated; MP: maternal plasma. Pool 1: 25.7% H28761, 54.7% H28986, 19.6% H90015. Pool 2: 15.2% H28761, 52.0% H28986, 32.8% H90015.

Supplementary Table 6: Observed COOH-THC Concentrations in Maternal Plasma, Placenta, and Fetal Tissue in Trimester 1 and 2 after Oral or Inhalation Consumption of Cannabis

Subject	MP (nM)	Fetal Brain (nM)	Fetal Brain/MP	Fetal Kidney (nM)	Fetal Kidney/MP	Fetal Liver (nM)	Fetal Liver/MP	Placenta Mean (nM)	Placenta/MP
H28680	24							6.3	0.26
H28688	134							46	0.35
H28761	295							22	0.075
H28869	68							11	0.16
H28928	171	24	0.14			67	0.39	29	0.17
H28960	88							19	0.22
H28972	25							BLOQ	
H28986	158							41	0.26
H28987	10							BLOQ	
H29026	30							BLOQ	
H29045	16							BLOQ	
H29110	202	15	0.074					21	0.10
H29122	331							BLOQ	
H29141	30							BLOQ	
H90004	242							91	0.38
H90006	58							16	0.27
H90015	278							43	0.16
H90020	65							BLOQ	
Pool 1	189	23	0.12						
Pool 2	76			48	0.63				
Mean ± SD (%CV)			0.11 ± 0.03 (31)						0.22 ± 0.096 (44)
H28718	135							27	0.20
H28786	55	11	0.20	17	0.32	32	0.59	BLOQ	
H28820	53							BLOQ	
H28870	205							30	0.15
H28894	147	17	0.11	29	0.20	72	0.49	23	0.16
H28896	3.1	BLOQ		BLOQ		BLOQ		BLOQ	
H28913	24							BLOQ	
H28983	128	22	0.17	22	0.17	49	0.38	38	0.30
H28998	17	BLOQ						37	2.2
H29046	18	BLOQ						BLOQ	
H29069	84	24	0.28	13	0.15	34	0.41	BLOQ	
H29075	1.9	BLOQ						BLOQ	
H29128	151							BLOQ	
H90000	134	24	0.18	32	0.24	73	0.54	40	0.30
H90003	76	BLOQ		12	0.15	29	0.38	25	0.33
H90005	58	2.9	0.050	7.6	0.13	16	0.27	BLOQ	
H90010	131	BLOQ		80	0.61	80	0.61	74	0.57
H90012	84							15	0.17
H90014	31	6.6	0.21	3.0	0.10	8.0	0.26	7.8	0.25
H90016	37	9.3	0.25	6.9	0.19	17	0.46	BLOQ	
H90018	334	35	0.10	91	0.27	171	0.51	BLOQ	
H90022	81	BLOQ		16	0.19	35	0.42	BLOQ	
Mean ± SD (%CV)			0.17 ± 0.07 (43)		0.23 ± 0.14 (60)		0.44 ± 0.11 (25)		0.46 ± 0.63 (136)

BLOQ: below limit of quantification; Blank rows: no sample collected and/or ratio cannot be calculated; MP: maternal plasma. Pool 1: 25.7% H28761, 54.7% H28986, 19.6% H90015. Pool 2: 15.2% H28761, 52.0% H28986, 32.8% H90015.

Supplementary Table 7: Non-pregnant PBPK Model Predicted and Observed Δ^9 -THC and 11-OH-THC Plasma Exposure (AUC_{inf} and C_{max}) after Various Routes of Δ^9 -THC Consumption

Intravenous												
	Ohlsson 1982*				Hunt and Jones 1980				Naef 2004			
	Δ^9 -THC (5 mg)		11-OH-THC		Δ^9 -THC (2 mg)		11-OH-THC		Δ^9 -THC (3.71 mg)		11-OH-THC	
	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)
Observed	213	256	N/A	N/A	369	112	N/A	N/A	868	293	27.6	41.4
Predicted	312	365	N/A	N/A	204	127	N/A	N/A	378	195	22.9	43.7
P/O	1.47	1.43	N/A	N/A	0.55	1.13	N/A	N/A	0.44	0.67	0.83	1.06
Acceptance Range	N	N	N/A	N/A	(0.10 – 7.39)	(0.62 – 1.96)	N/A	N/A	(0.08 – 5.82)	(0.44 – 1.40)	N/A	N/A
Inhalation												
	Ohlsson 1982*				McBurney 1986							
	Δ^9 -THC (9.44 mg)		11-OH-THC		Δ^9 -THC (10.5 mg)		11-OH-THC					
	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)				
Observed	79.9	103	N/A	N/A	271	245	N/A	N/A				
Predicted	88.2	130	N/A	N/A	149	110	N/A	N/A				
P/O	1.10	1.27	N/A	N/A	0.55	0.45	N/A	N/A				
Acceptance Range	N	N	N/A	N/A	(0.26 – 0.65)	(0.18 – 0.58)	N/A	N/A				
Oral												
	Oh 2017*				Lunn 2019				Parikh 2016			
	Δ^9 -THC (5 mg)		11-OH-THC		Δ^9 -THC (10 mg)		11-OH-THC		Δ^9 -THC (4.25 mg)		11-OH-THC	
	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)	C _{max} (nM)	AUC _{inf} (nM*h)
Observed	3.79	15.5	6.49	35.9	7.44	25.6	9.70	46.6	4.26	12.3	6.75	31.7
Predicted	3.59	15.5	4.70	26.3	6.88	29.8	13.7	68.8	2.93	13.1	5.82	29.7
P/O	0.94	1.00	0.72	0.73	0.92	1.16	1.41	1.48	0.69	1.07	0.86	0.94
Acceptance Range	N	N	N	N	(0.73 – 1.72)	(0.88 – 1.41)	(0.74 – 2.38)	(0.77 – 2.47)	(0.54 – 1.28)	(0.78 – 1.25)	(0.45 – 1.45)	(0.48 – 1.54)
Drug-Drug Interactions and Genetic Polymorphism												
	Stott 2013				Sativex: Summary of Product Characteristic				Sachse-Seeboth 2009			
	10.8 mg Δ^9 -THC + 400 mg Ketoconazole		11-OH-THC		Δ^9 -THC (15 mg)		11-OH-THC		10.8 mg Δ^9 -THC + 200 mg BID Fluconazole		11-OH-THC	
	C _{max} R	AUC _{inf} R	C _{max} R	AUC _{inf} R	C _{max} R	AUC _{inf} R	C _{max} R	AUC _{inf} R	C _{max} R	AUC _{inf} R	C _{max} R	AUC _{inf} R
Observed	1.20	1.88	N/A	N/A	1.22	1.32	N/A	N/A	2.33	3.09	N/A	N/A
Predicted	1.71	1.70	N/A	N/A	1.52	1.72	N/A	N/A	2.63	3.56	N/A	N/A
P/O	1.43	0.90	N/A	N/A	1.25	1.30	N/A	N/A	1.13	1.15	N/A	N/A
Acceptance Range	(0.41 – 2.42)	(0.61 – 1.65)	N/A	N/A	(0.41 – 2.41)	(0.67 – 1.50)	N/A	N/A	(0.32 – 1.54)	(0.45 – 1.46)	N/A	N/A

N/A: data not available; N: not applicable as this dataset was used as a training dataset; C_{max} : maximum concentration; AUC_{inf} : area under the plasma concentration-time curve to time infinity; BID: dosed two times per day. *The Ohlsson 1982 and Oh 2017 data sets were used as the training data sets while the remainder were used as verification data sets; Δ^9 -THC molecular weight = 314.45 g/mol.

Supplementary Table 8: m-f-PBPK Model Predicted and Observed Umbilical Venous Plasma and Fetal Tissue Δ⁹-THC Concentration Relative to Maternal Plasma in Trimester 2 and 3 Pregnancy after Inhalation and Oral Consumption of Δ⁹-THC

	Trimester 2			Trimester 3
	Fetal Brain/MP	Fetal Kidney/MP	Fetal Liver/MP	UVP/MP
Observed*	0.39 (63%)	0.44 (49%)	1.18 (54%)	0.33 (38%)
Acceptance Range	(0.20 – 0.75)	(0.22 – 0.88)	(0.62 – 2.25)	(0.23 – 0.47)
Predicted	0.54	0.73	1.8	0.31

*Data are Geometric Mean (%CV); MP: maternal plasma; UVP: umbilical venous plasma. The predicted values were at 12 hours; post-absorption when distributional equilibrium between plasma and tissue concentrations is expected to be reached, i.e. >12 hours.

Supplementary Table 9: LC-MS/MS parameters for Drug Quantification

A. LC gradient program

Time (min)	Flow Rate (mL/min)	A (water with 0.2% acetic acid)	B (acetonitrile with 0.2% acetic acid)
0	0.3	90	10
0.5	0.3	90	10
2	0.3	5	95
4	0.3	5	95
4.1	0.3	90	10
4.5	0.3	90	10

B. APCI MS/MS parameters

Compound	Parent Ion (m/z)	Product Ion (m/z)	Collision Energy (V)
Δ^9 -THC	315.3	193.2	22
d3- Δ^9 -THC	318.3	196.3	20
11-OH-THC	331.3	193.2	26
d3-11-OH-THC	334.3	196.3	26
COOH-THC	345.3	327.3	20
d3-COOH-THC	348.3	330.3	20

References

- 1 Ohlsson, A. *et al.* Single dose kinetics of deuterium labelled delta 1-tetrahydrocannabinol in heavy and light cannabis users. *Biomed Mass Spectrom* **9**, 6-10, doi:10.1002/bms.1200090103 (1982).
- 2 Hunt, C. A. & Jones, R. T. Tolerance and disposition of tetrahydrocannabinol in man. *J Pharmacol Exp Ther* **215**, 35-44 (1980).
- 3 Naef, M., Russmann, S., Petersen-Felix, S. & Brenneisen, R. Development and pharmacokinetic characterization of pulmonary and intravenous delta-9-tetrahydrocannabinol (THC) in humans. *J Pharm Sci* **93**, 1176-1184, doi:10.1002/jps.20037 (2004).
- 4 McBurney, L. J., Bobbie, B. A. & Sepp, L. A. GC/MS and EMIT analyses for delta 9-tetrahydrocannabinol metabolites in plasma and urine of human subjects. *J Anal Toxicol* **10**, 56-64, doi:10.1093/jat/10.2.56 (1986).
- 5 Oh, D. A., Parikh, N., Khurana, V., Cognata Smith, C. & Vetticaden, S. Effect of food on the pharmacokinetics of dronabinol oral solution versus dronabinol capsules in healthy volunteers. *Clin Pharmacol* **9**, 9-17, doi:10.2147/CPAA.S119676 (2017).
- 6 Lunn, S. *et al.* Human Pharmacokinetic Parameters of Orally Administered Delta(9)-Tetrahydrocannabinol Capsules Are Altered by Fed Versus Fasted Conditions and Sex Differences. *Cannabis Cannabinoid Res* **4**, 255-264, doi:10.1089/can.2019.0037 (2019).
- 7 Parikh, N., Kramer, W. G., Khurana, V., Cognata Smith, C. & Vetticaden, S. Bioavailability study of dronabinol oral solution versus dronabinol capsules in healthy volunteers. *Clin Pharmacol* **8**, 155-162, doi:10.2147/CPAA.S115679 (2016).
- 8 Thomas, B. F., Compton, D. R. & Martin, B. R. Characterization of the lipophilicity of natural and synthetic analogs of delta 9-tetrahydrocannabinol and its relationship to pharmacological potency. *J Pharmacol Exp Ther* **255**, 624-630 (1990).
- 9 Giroud, C. *et al.* Delta(9)-THC, 11-OH-Delta(9)-THC and Delta(9)-THCCOOH plasma or serum to whole blood concentrations distribution ratios in blood samples taken from living and dead people. *Forensic Sci Int* **123**, 159-164, doi:10.1016/s0379-0738(01)00538-2 (2001).
- 10 Patilea-Vrana, G. I. & Unadkat, J. D. Quantifying Hepatic Enzyme Kinetics of (-)-(9)-Tetrahydrocannabinol (THC) and Its Psychoactive Metabolite, 11-OH-THC, through In Vitro Modeling. *Drug Metab Dispos* **47**, 743-752, doi:10.1124/dmd.119.086470 (2019).
- 11 Kemp, P. M., Cardona, P. S., Chaturvedi, A. K. & Soper, J. W. Distribution of $\Delta(9)$ -Tetrahydrocannabinol and 11-Nor-9-Carboxy- $\Delta(9)$ -Tetrahydrocannabinol Acid in Postmortem Biological Fluids and Tissues From Pilots Fatally Injured in Aviation Accidents. *J Forensic Sci* **60**, 942-949, doi:10.1111/1556-4029.12751 (2015).
- 12 Saenz, S. R., Lewis, R. J., Angier, M. K. & Wagner, J. R. Postmortem Fluid and Tissue Concentrations of THC, 11-OH-THC and THC-COOH. *J Anal Toxicol* **41**, 508-516, doi:10.1093/jat/bkx033 (2017).
- 13 Cliburn, K. D., Huestis, M. A., Wagner, J. R. & Kemp, P. M. Cannabinoid distribution in fatally-injured pilots' postmortem fluids and tissues. *Forensic Sci Int* **329**, 111075, doi:10.1016/j.forsciint.2021.111075 (2021).
- 14 Mura, P., Kintz, P., Dumestre, V., Raul, S. & Hauet, T. THC can be detected in brain while absent in blood. *J Anal Toxicol* **29**, 842-843, doi:10.1093/jat/29.8.842 (2005).
- 15 Withey, S. L., Bergman, J., Huestis, M. A., George, S. R. & Madras, B. K. THC and CBD blood and brain concentrations following daily administration to adolescent primates. *Drug Alcohol Depend* **213**, 108129, doi:10.1016/j.drugalcdep.2020.108129 (2020).
- 16 Kumar, A. R., Patilea-Vrana, G. I., Anoshchenko, O. & Unadkat, J. D. Characterizing and Quantifying Extrahepatic Metabolism of (-)-Delta(9)-Tetrahydrocannabinol (THC) and Its Psychoactive Metabolite, (+/-)-11-Hydroxy-Delta(9)-THC (11-OH-THC). *Drug Metab Dispos* **50**, 734-740, doi:10.1124/dmd.122.000868 (2022).
- 17 Kumar, A. R. *et al.* Understanding the Mechanism and Extent of Transplacental Transfer of (-)- $\Delta(9)$ - Tetrahydrocannabinol (THC) in the Perfused Human Placenta to Predict In Vivo Fetal THC Exposure. *Clin Pharmacol Ther* **114**, 446-458, doi:10.1002/cpt.2964 (2023).