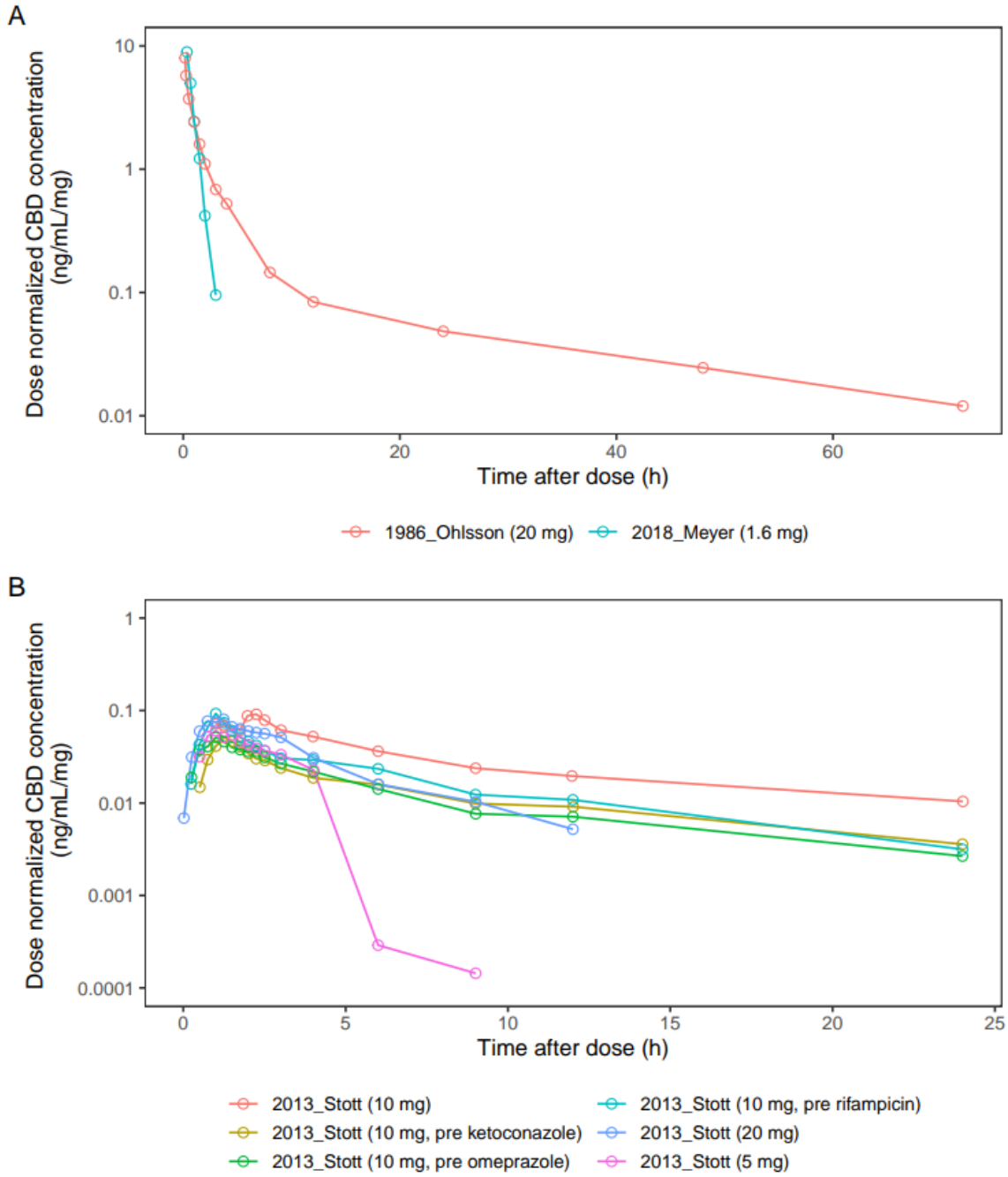
## SUPPLEMENTARY MATERIALS



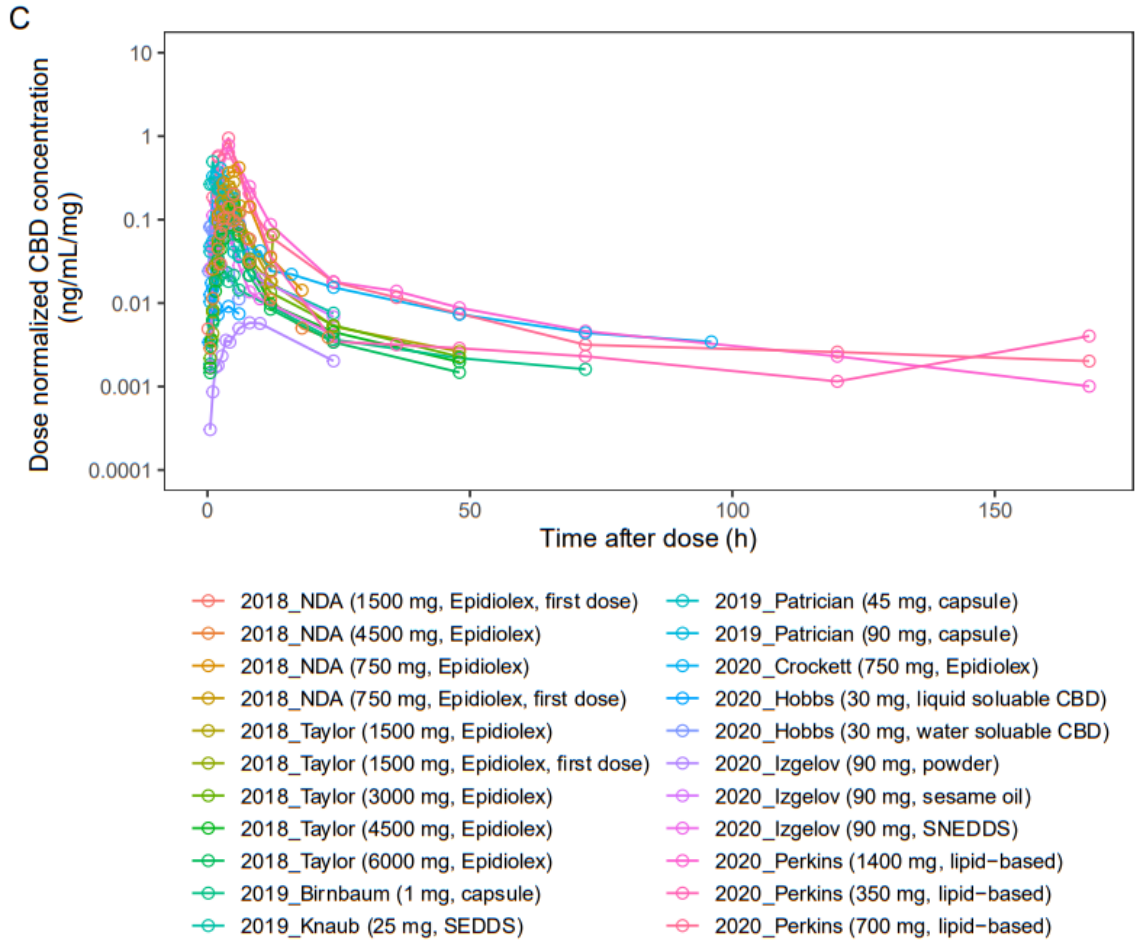
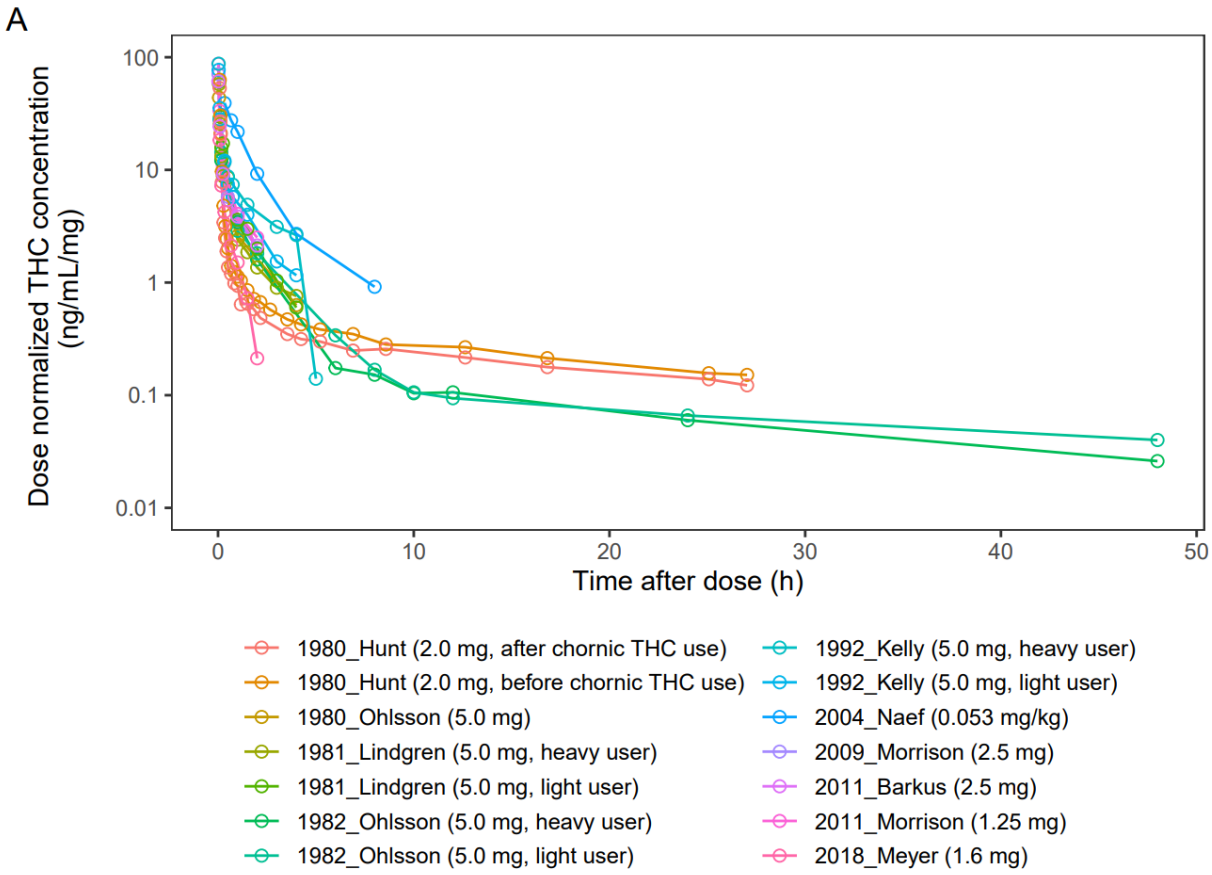
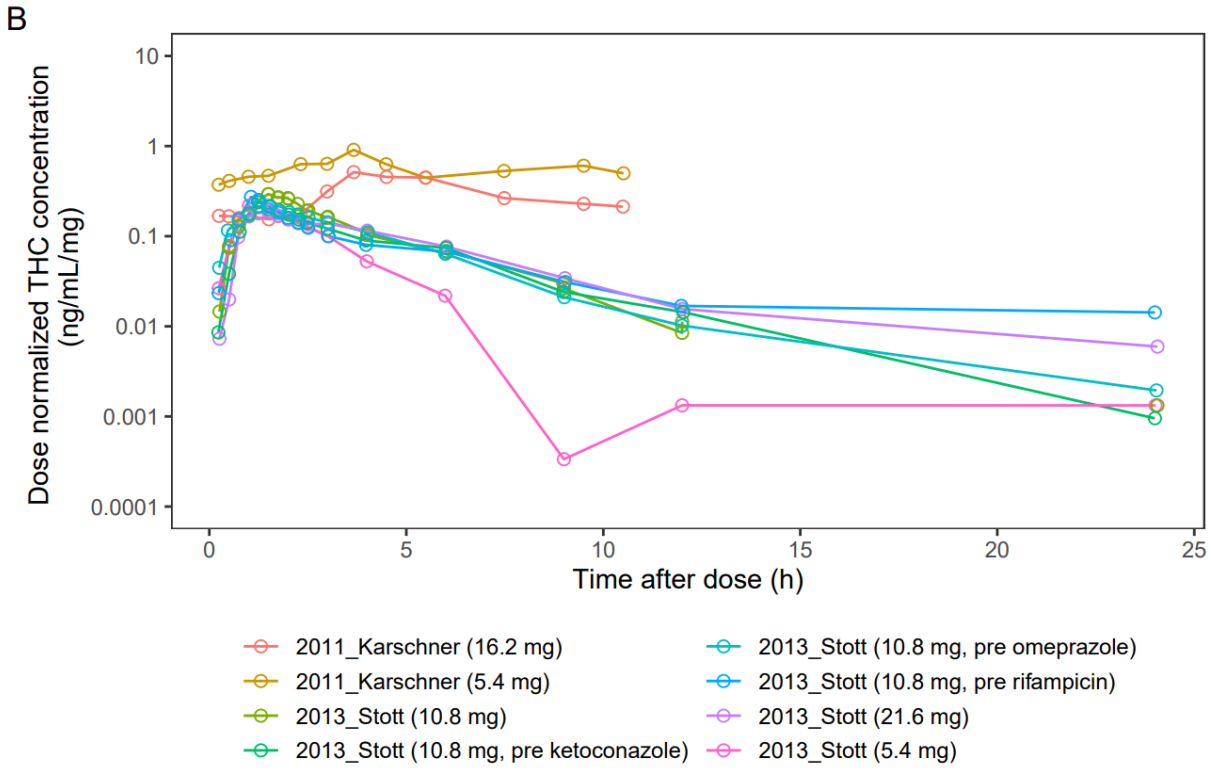
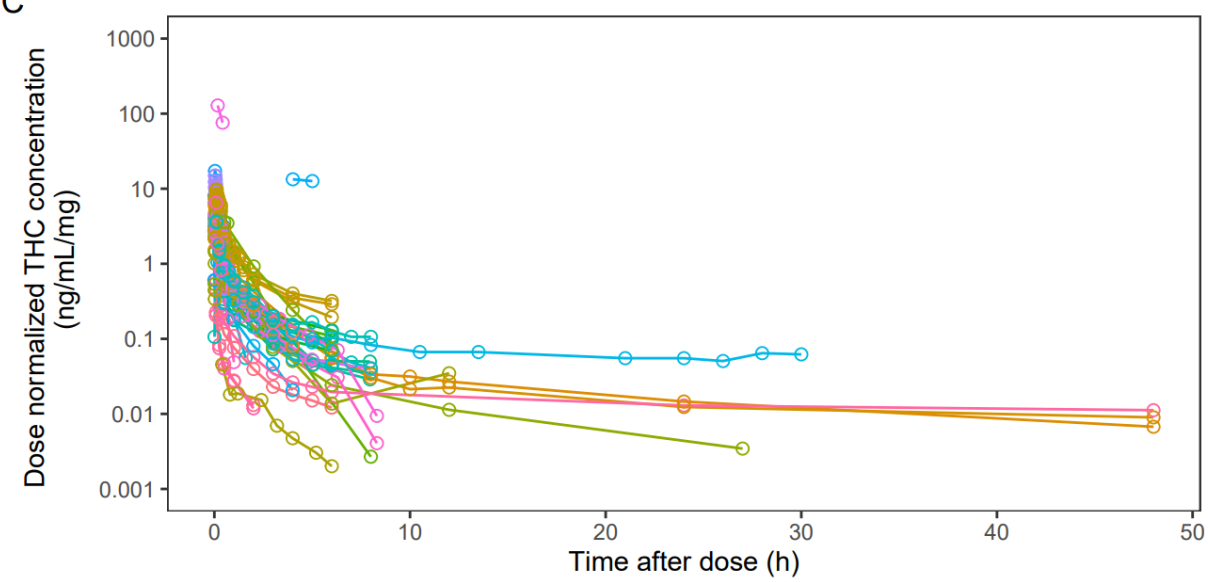



**Figure S1.** Dose-normalized observed cannabidiol (CBD) concentration vs. time profiles following (**A**) intravenous (IV) administration, (**B**) oromucosal spray administration, and (**C**) oral administration. If profiles of different replicates in the same study were reported, they would be noted on the labels. Formulations of oral CBD were also noted on the labels. SEDDS, self-emulsifying drug delivery systems; first dose, concentration of the first dose when given as repeat doses.


A
Dose normalized THC concentration (ng/mL/mg)
100
10
1
0.1
0.01
0
10
20
30
40
50
Time after dose (h)
1980_Hunt (2.0 mg, after chornic THC use)
1980_Hunt (2.0 mg, before chornic THC use)
1980_Ohlsson (5.0 mg)
1981_Lindgren (5.0 mg, heavy user)
1981_Lindgren (5.0 mg, light user)
1982_Ohlsson (5.0 mg, heavy user)
1982_Ohlsson (5.0 mg, light user)
1992_Kelly (5.0 mg, heavy user)
1992_Kelly (5.0 mg, light user)
2004_Naef (0.053 mg/kg)
2009_Morrison (2.5 mg)
2011_Barkus (2.5 mg)
2011_Morrison (1.25 mg)
2018_Meyer (1.6 mg)


B
Dose normalized THC concentration (ng/mL/mg)
10
1
0.1
0.01
0.001
0.0001
0
5
10
15
20
25
Time after dose (h)
2011_Karschner (16.2 mg)
2011_Karschner (5.4 mg)
2013_Stott (10.8 mg)
2013_Stott (10.8 mg, pre ketoconazole)
2013_Stott (10.8 mg, pre omeprazole)
2013_Stott (10.8 mg, pre rifampicin)
2013_Stott (21.6 mg)
2013_Stott (5.4 mg)

C




- 1980_Ohlsson (13.0 mg)
- 1981_Lindgren (12.7 mg, heavy user)
- 1981_Lindgren (13.4 mg, light user)
- 1982_Barnett (8.94 mg)
- 1982_Ohlsson (8.9 mg, heavy user)
- 1982_Ohlsson (8.9 mg, light user)
- 1982_Perez−Reyes (12.8 mg)
- 1982_Perez−Reyes (16.0 mg)
- 1982_Perez−Reyes (9.7 mg)
- 1988_Johansson (15.0 mg)
- 1992_Huestis (15.8 mg)
- 1992_Huestis (33.8 mg)
- 1994_Mattes (2.54 mg)
- 2004_Naef (0.053 mg/kg)
- 2007_Abrams (15.3 mg, smoked)
- 2007_Abrams (15.3 mg, vapourized)
- 2007_Abrams (30.6 mg, smoked)
- 2007_Abrams (30.6 mg, vapourized)
- 2007_Abrams (61.2 mg, smoked)
- 2007_Abrams (61.2 mg, vapourized)
- 2008_Hunault (29.3 mg)
- 2008_Hunault (49.1 mg)
- 2008_Hunault (69.4 mg)
- 2008_Toennes (0.5 mg/kg, heavy user)
- 2008_Toennes (0.5 mg/kg, light user)
- 2011_Abrams (32.4 mg)
- 2011_Schwope (54.0 mg)
- 2014_Desrosiers (54.0 mg, heavy user)
- 2014_Desrosiers (54.0 mg, light user)
- 2014_Eisenberg (3.08 mg, subject #1)
- 2014_Eisenberg (3.08 mg, subject #2)
- 2014_Eisenberg (3.08 mg, subject #3)
- 2014_Eisenberg (3.08 mg, subject #4)
- 2014_Eisenberg (3.08 mg, subject #5)
- 2014_Eisenberg (3.08 mg, subject #6)
- 2014_Eisenberg (3.08 mg, subject #7)
- 2014_Eisenberg (3.08 mg, subject #8)
- 2014_Hunault (29.3 mg)
- 2014_Hunault (49.1 mg)
- 2014_Hunault (69.4 mg)
- 2015_Hartman (0.03 mg)
- 2015_Hartman (14.5 mg)
- 2015_Hartman (33.5 mg)
- 2018_Meyer (1.6 mg)
- 2019_Brands (70.3 mg)
- 2019_Brands (94.0 mg)
- 2020_Matheson (73.3 mg, women)
- 2020_Matheson (86.0 mg, men)

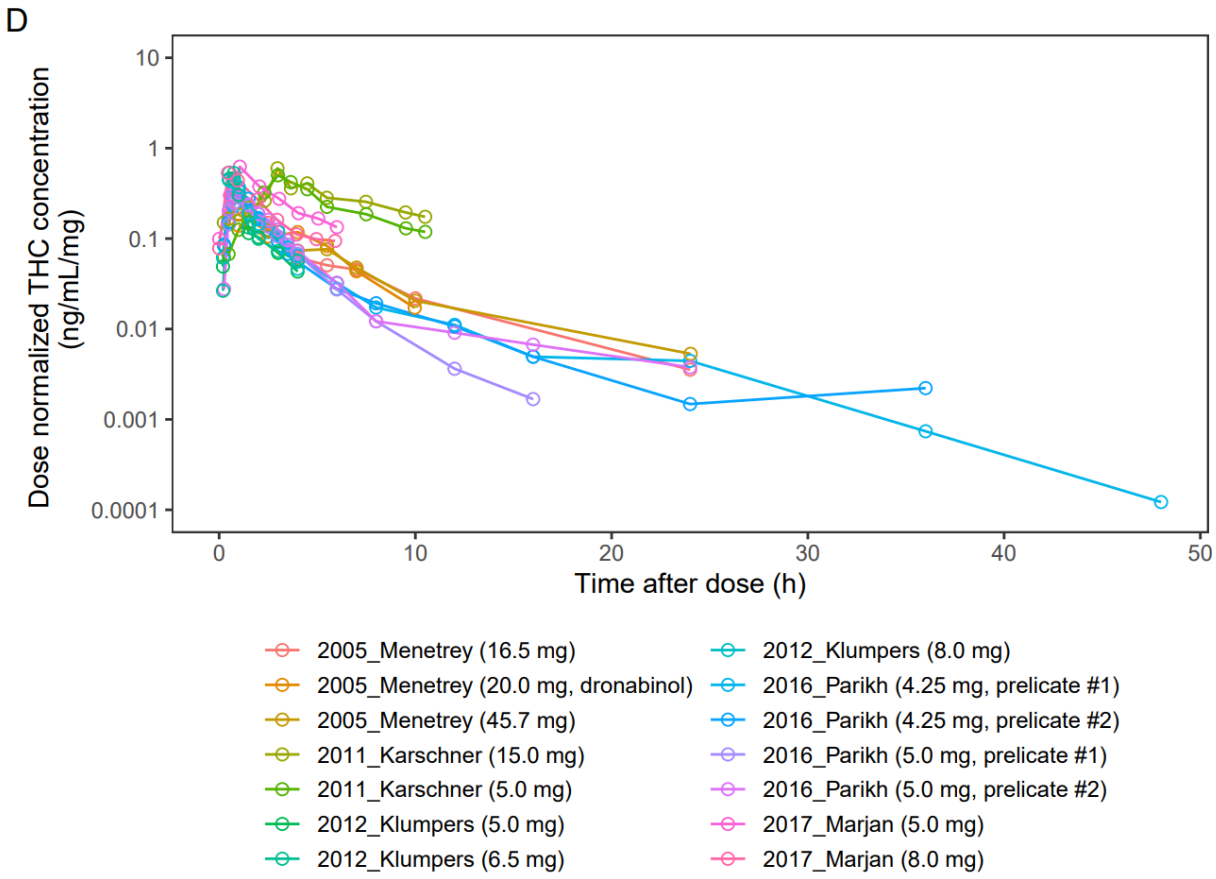



**Figure S2.** Dose-normalized observed delta-9-tetrahydrocannabinol (THC) concentration profiles following (**A**) IV administration, (**B**) oromucosal spray administration, (**C**) inhalation administration, and (**D**) oral administration. If concentration profiles of different subjects, replicates, or THC exposure frequency in the same study were reported, they would be noted on the labels.

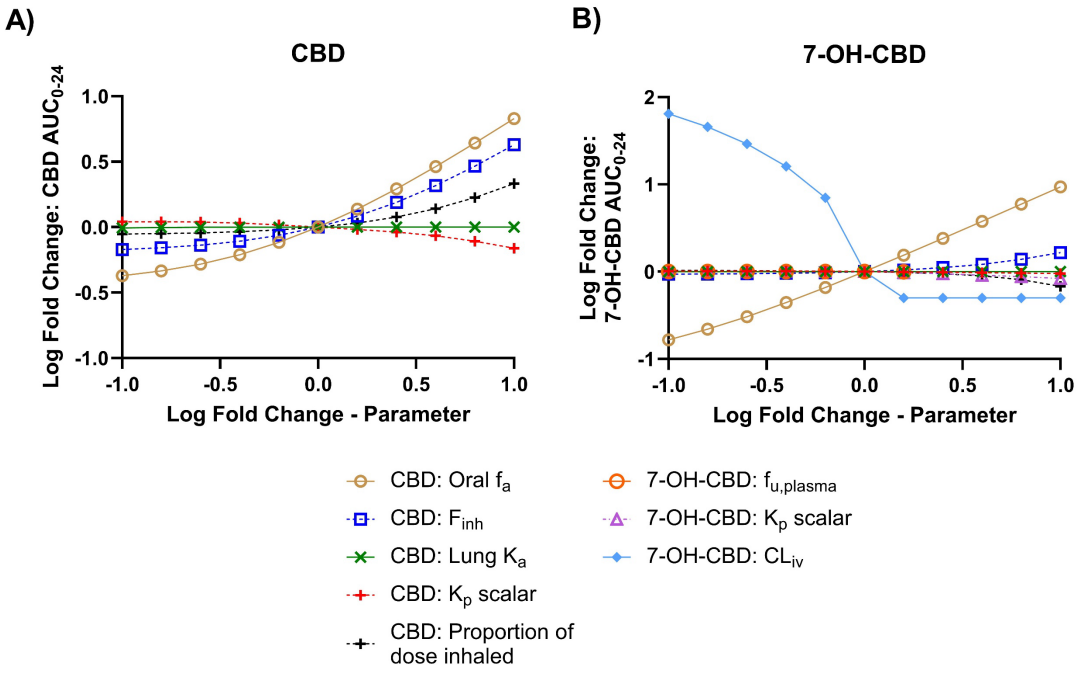



**Figure S3.** Sensitivity analyses assessing the impact of various PBPK model parameters on the area under the concentration-time curve from 0 to 24 h ($AUC_{0\text{-}24}$) for (**A**) CBD and (**B**) 7-OH-CBD. Oral $f_a$, fraction absorbed from the oral dose; $F_{inh}$, fraction of drug absorbed from the inhalation; Lung $k_a$, first-order lung absorption rate constant; $K_p$ scalar, scalar applied to predicted tissue $K_p$ values; $f_{u,plasma}$, fraction unbound in plasma; $CL_{iv}$, intravenous clearance.

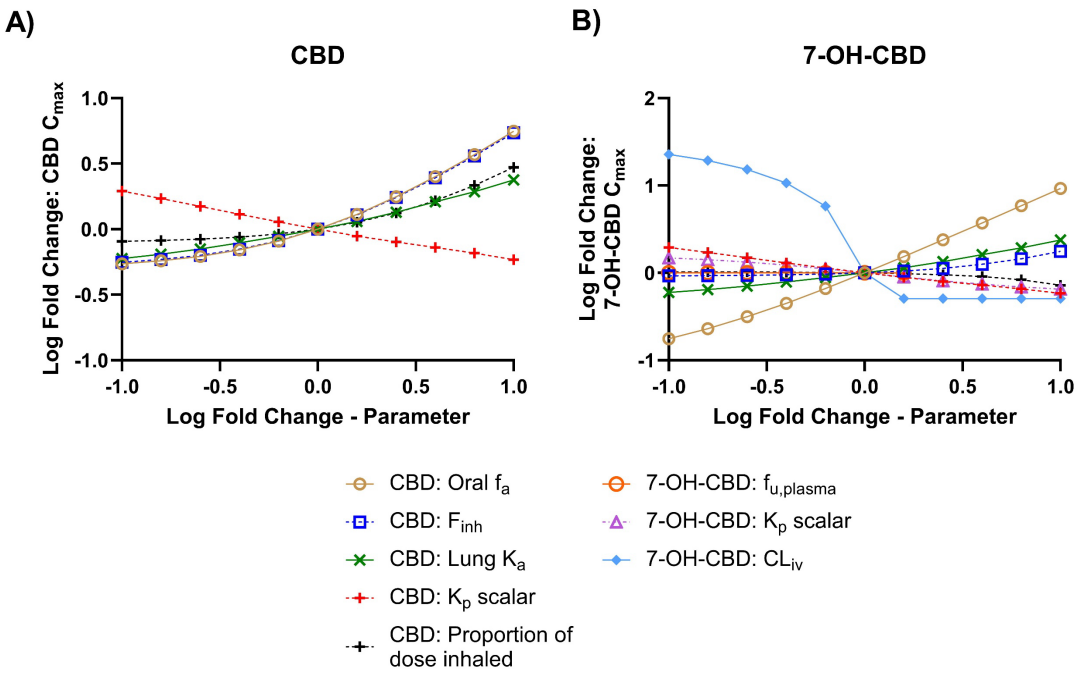



**Figure S4.** Sensitivity analyses assessing the impact of various PBPK model parameters on the peak concentration ($C_{max}$) of (**A**) CBD and (**B**) 7-OH-CBD. Oral $f_a$, fraction absorbed from the oral dose; $F_{inh}$, fraction of drug absorbed from the inhalation; Lung $k_a$, first-order lung absorption rate constant; $K_p$ scalar, scalar applied to predicted tissue $K_p$ values; $f_{u,plasma}$, fraction unbound in plasma; $CL_{iv}$, intravenous clearance.

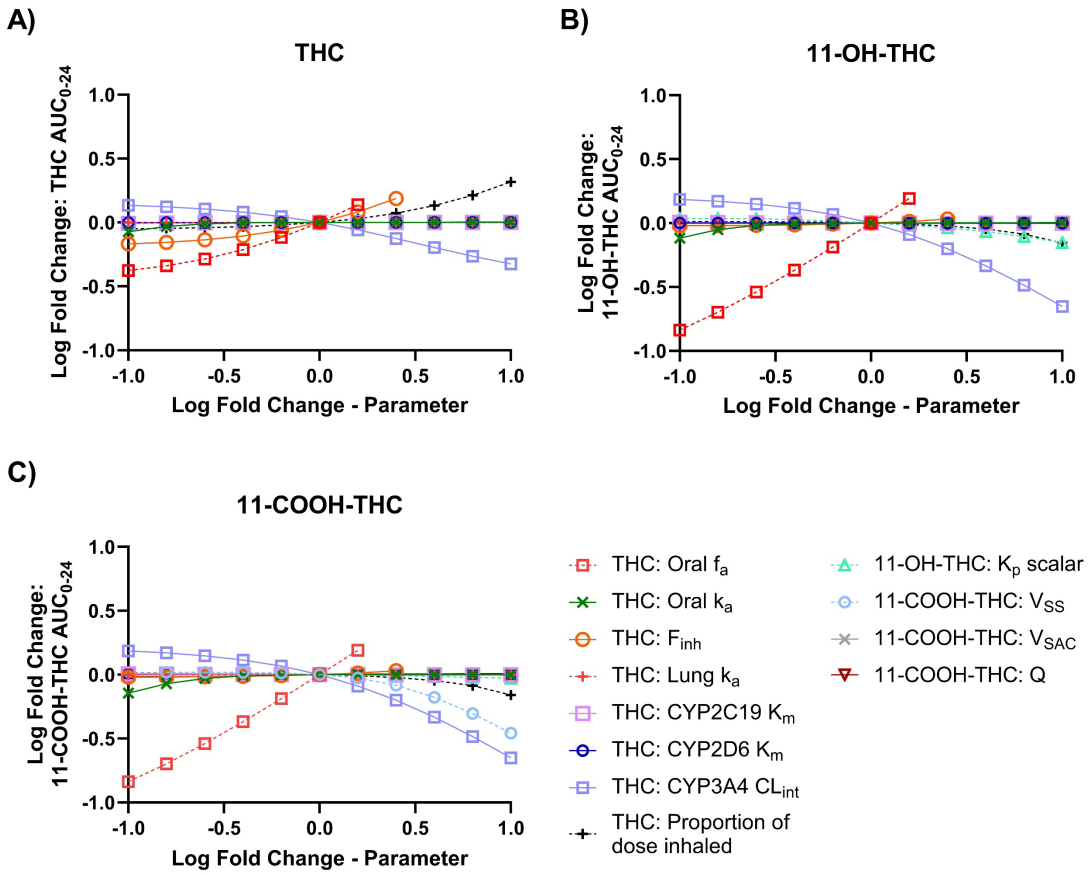



**Figure S5.** Sensitivity analyses assessing the impact of various PBPK model parameters on $AUC_{0-24}$ for (**A**) THC, (**B**) 11-OH-THC, and (**C**) 11-COOH-THC. Oral $f_a$, fraction absorbed from the oral dose; oral $k_a$, first-order absorption rate constant; $F_{inh}$, fraction of drug absorbed from the inhalation; Lung $k_a$, first-order lung absorption rate constant; $K_m$, Michaelis constant; $CL_{int}$, *in vitro* intrinsic clearance; $V_{ss}$, volume of distribution at steady state; $V_{sac}$, volume of the single adjusting compartment; Q, intercompartmental clearance.

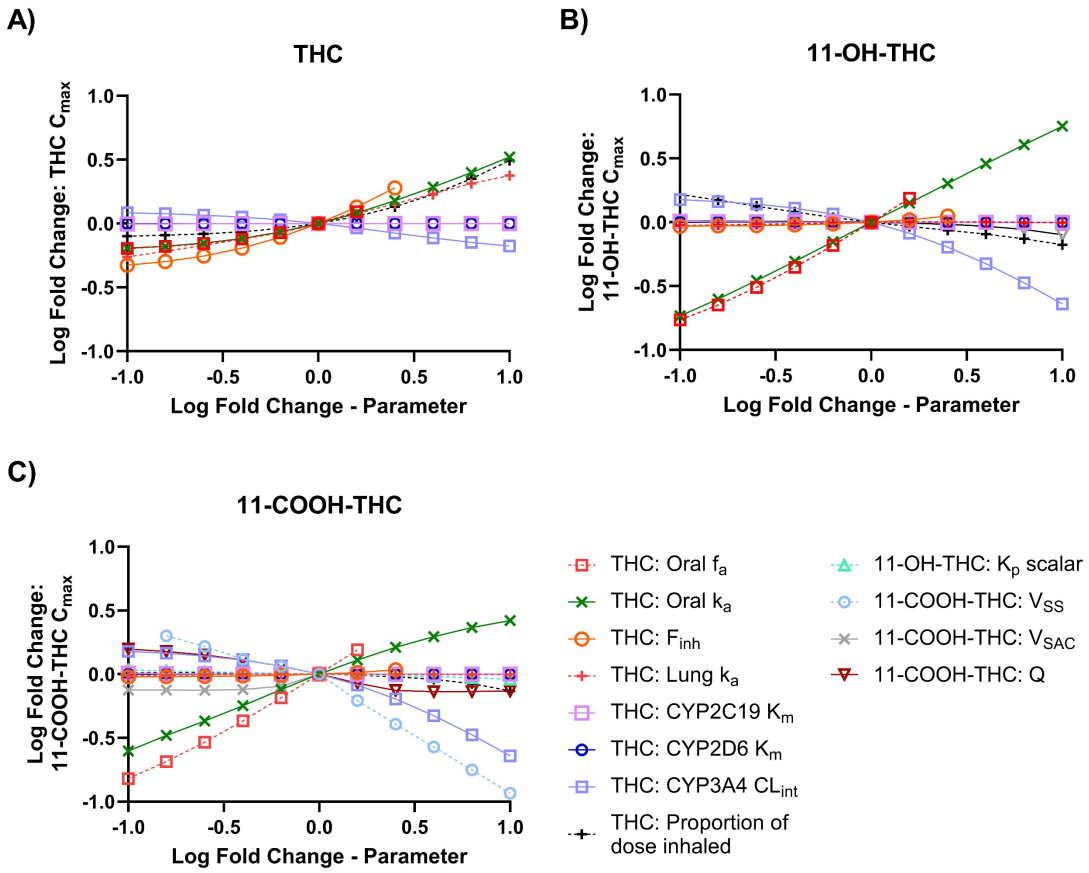



**Figure S6.** Sensitivity analyses assessing the impact of various PBPK model parameters on $C_{max}$ of (**A**) THC, (**B**) 11-OH-THC, and (**C**) 11-COOH-THC. Oral $f_a$, fraction absorbed from the oral dose; oral $k_a$, first-order absorption rate constant; $F_{inh}$, fraction of drug absorbed from the inhalation; Lung $k_a$, first-order lung absorption rate constant; $K_m$, Michaelis constant; $CL_{int}$, *in vitro* intrinsic clearance; $V_{ss}$, volume of distribution at steady state; $V_{sac}$, volume of the single adjusting compartment; Q, intercompartmental clearance.

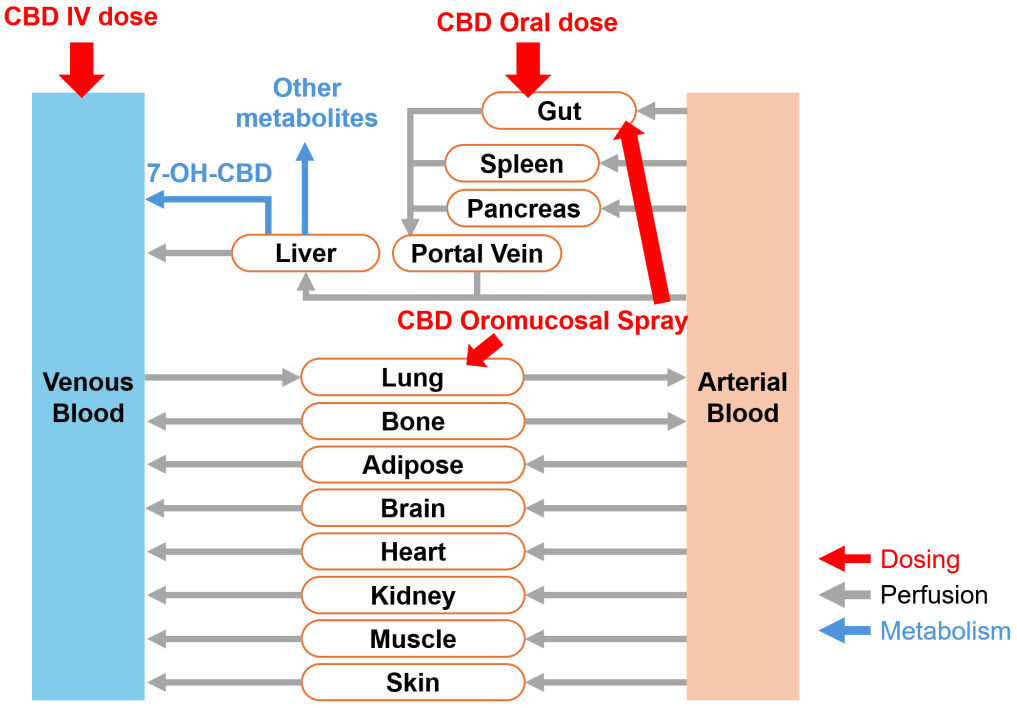



**Figure S7.** Schematic diagram of the organ compartments used in the whole-body physiologically based pharmacokinetic (PBPK) model for CBD and 7-OH-CBD. 7-OH-CBD is metabolized from CBD in the liver and enters the systemic circulation.

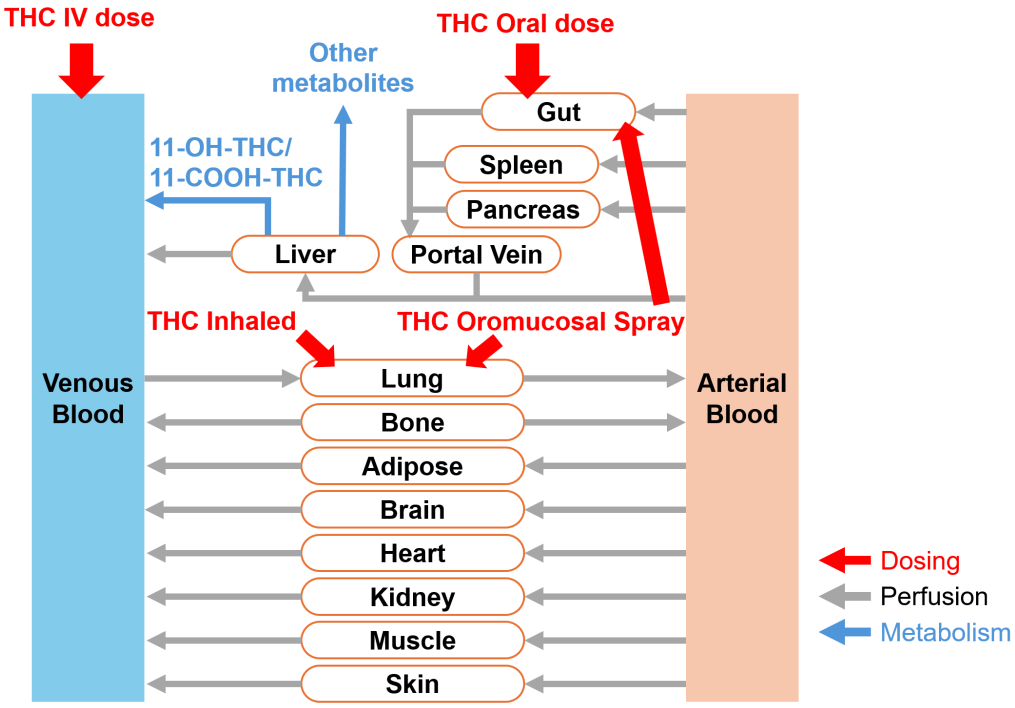



**Figure S8.** Schematic diagram of the organ compartments used in the whole-body PBPK model for THC and 11-OH-THC. 11-OH-THC is metabolized from THC in the liver and enters the systemic circulation.

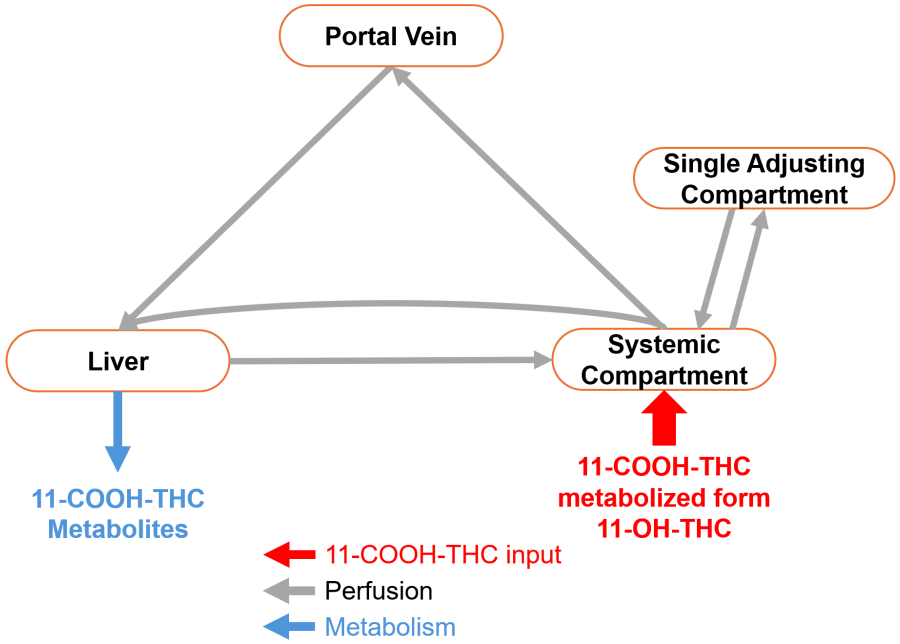



**Figure S9.** Schematic diagram of the compartments used in the minimal PBPK model for 11-COOH-THC. 11-COOH-THC is metabolized from 11-OH-THC in liver.

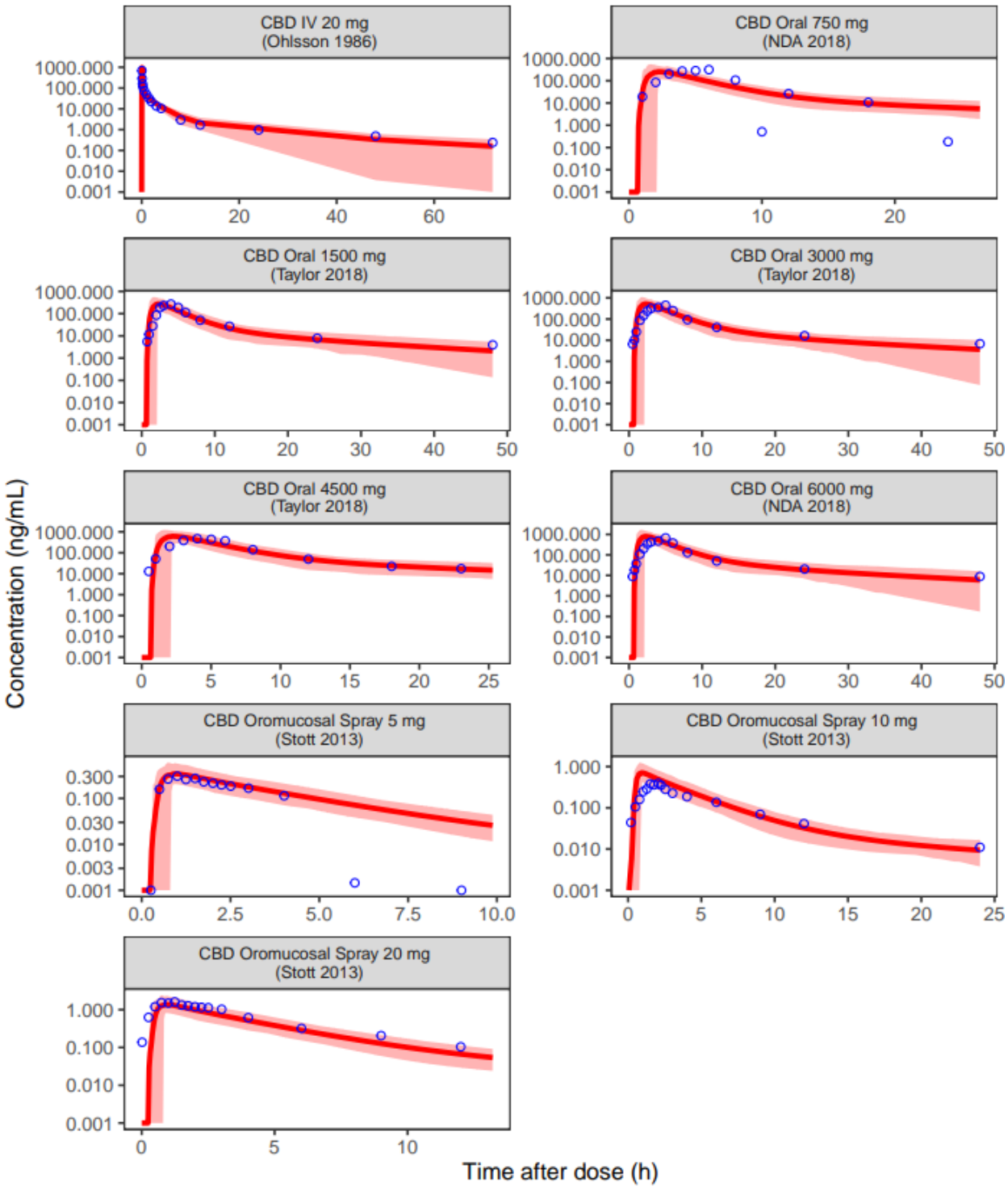



**Figure S10.** Observed and PBPK model-predicted CBD plasma concentrations. The red shaded areas represent the 5$^{th}$ to 95$^{th}$ percentiles of predicted values. The red lines and blue circles represent the mean predicted value and observed concentrations, respectively.

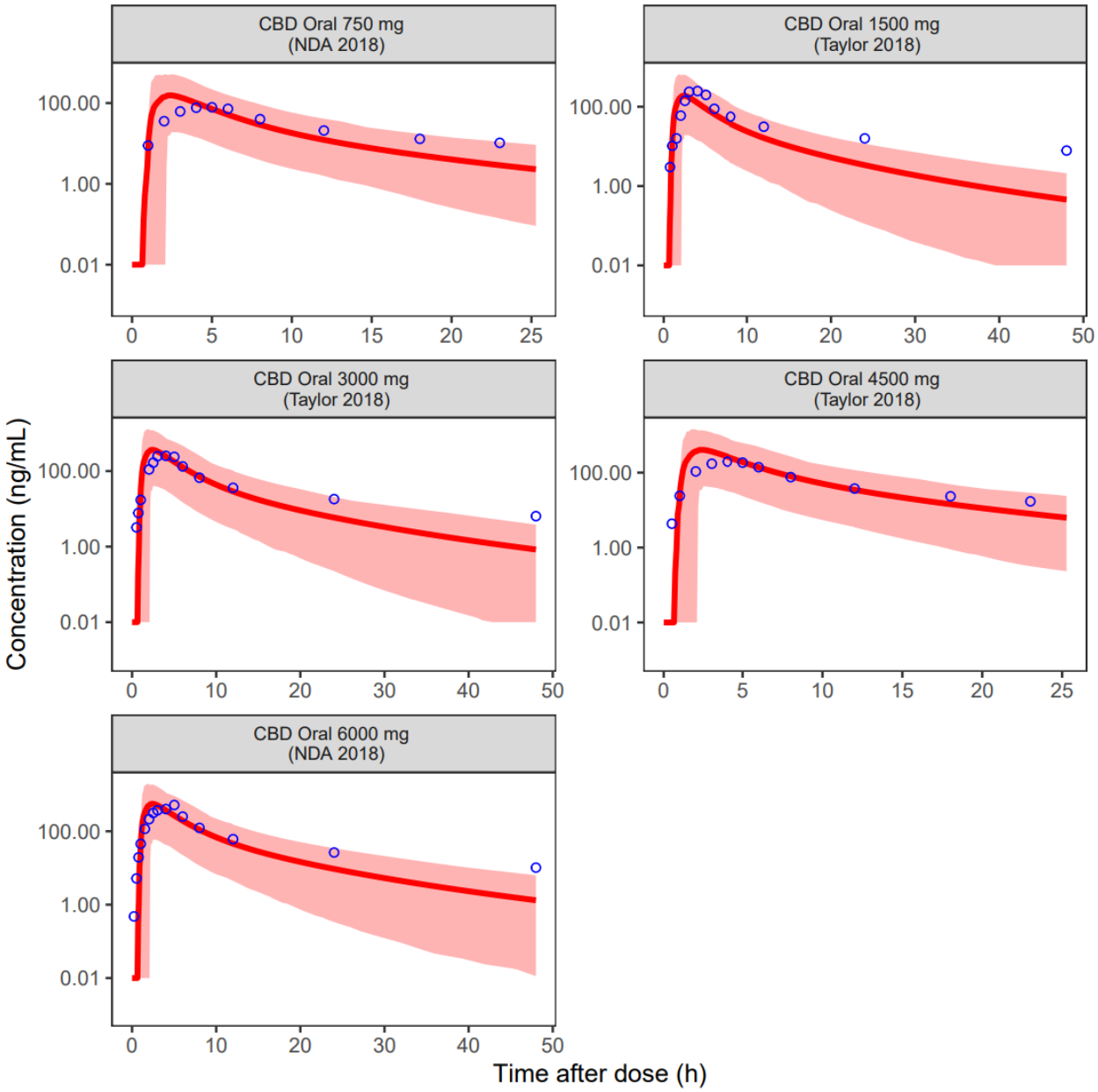



**Figure S11.** Observed and PBPK model-predicted 7-OH-CBD plasma concentrations. The red shaded areas represent the 5$^{th}$ to 95$^{th}$ percentiles of predicted values. The red lines and blue circles represent the mean predicted value and observed concentrations, respectively.

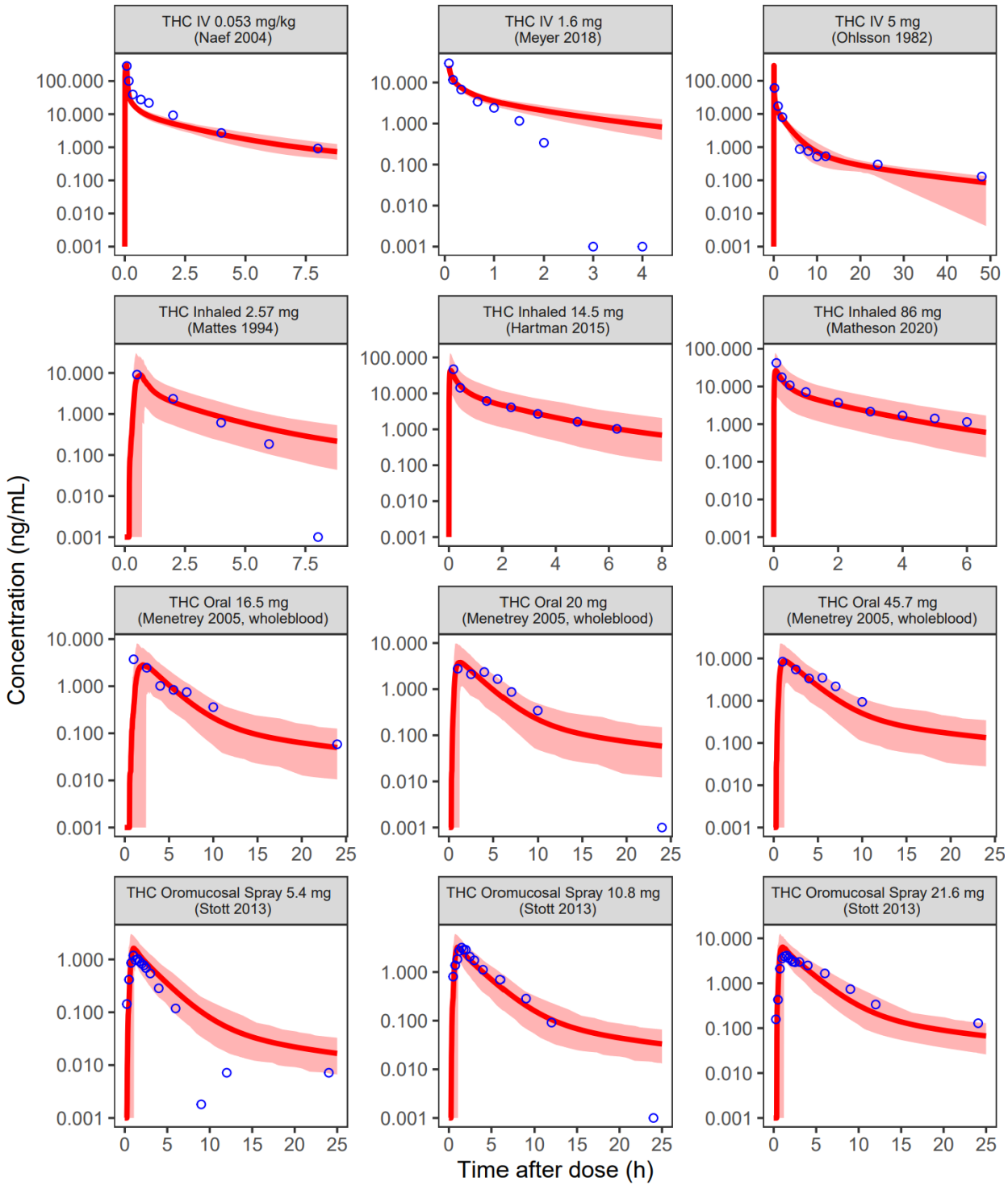



**Figure S12.** Observed and PBPK model-predicted THC plasma concentrations. If labeled with whole blood, the whole blood concentration was illustrated. The red shaded areas represent the 5$^{th}$ to 95$^{th}$ percentiles of predicted values. The red lines and blue circles represent the mean predicted value and observed concentrations, respectively.

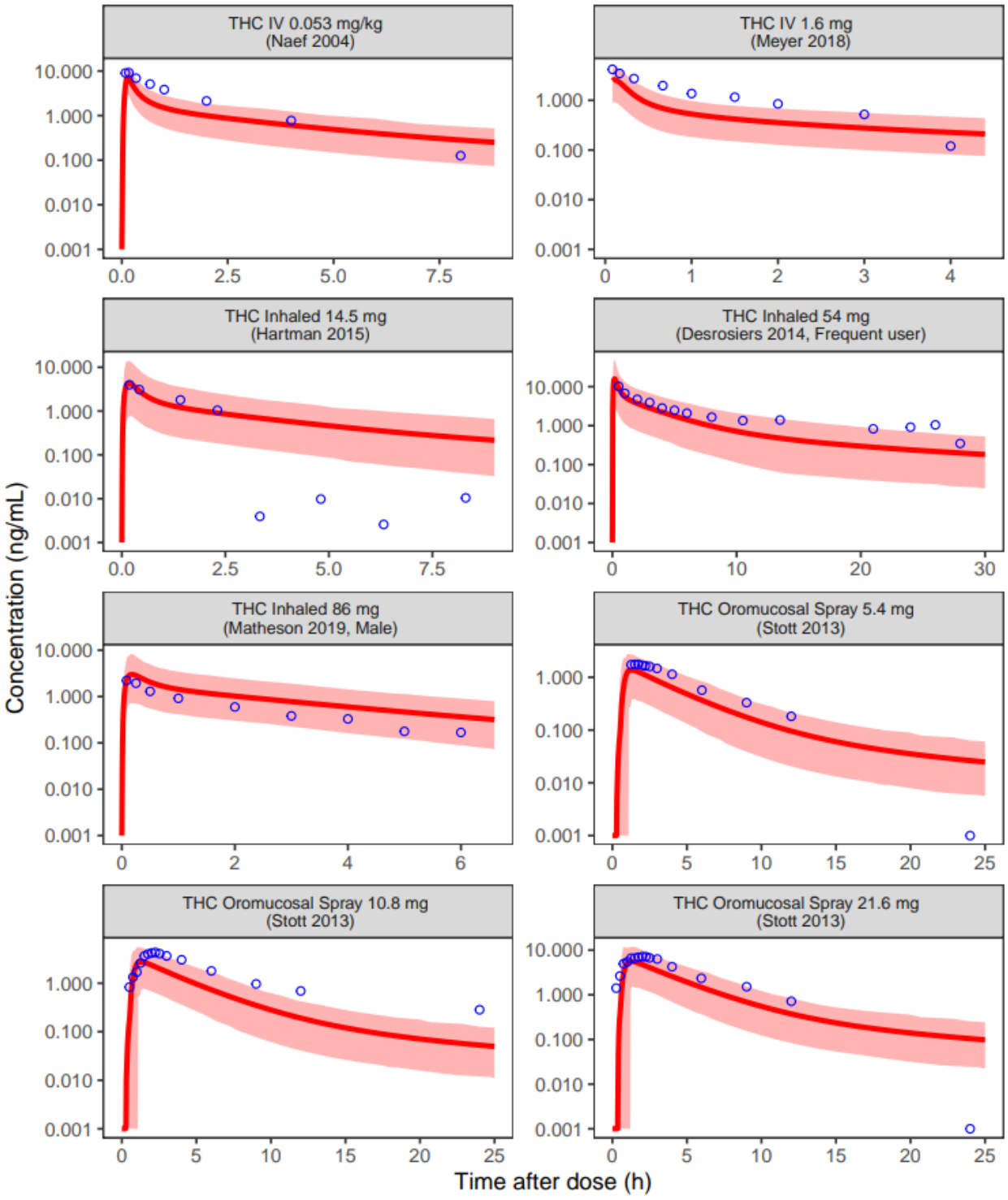



**Figure S13.** Observed and PBPK model-predicted 11-OH-THC plasma concentrations. The red shaded areas represent the 5$^{th}$ to 95$^{th}$ percentiles of predicted values. The red lines and blue circles represent the mean predicted value and observed concentrations, respectively.

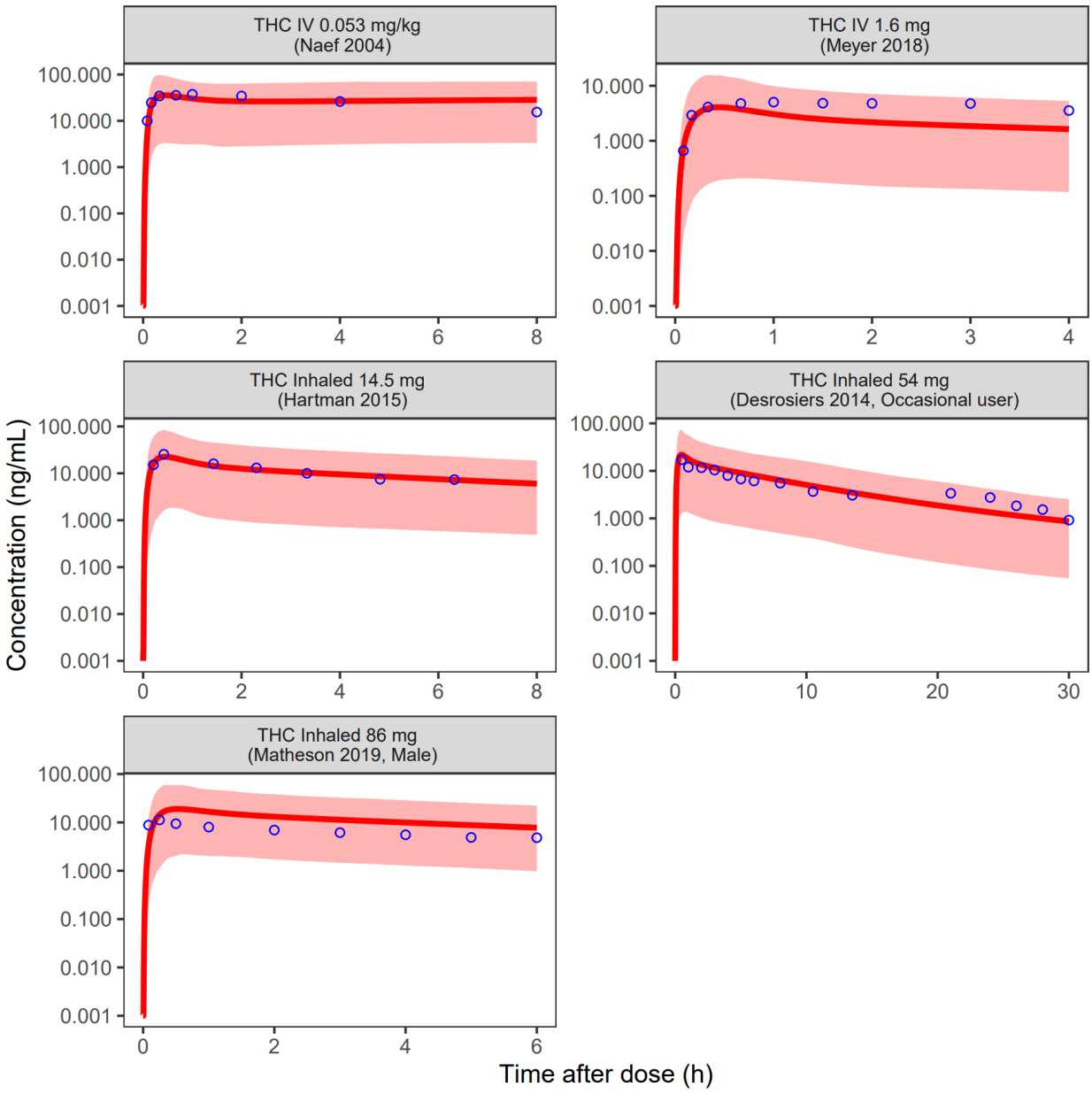



**Figure S14.** Observed and PBPK model-predicted 11-COOH-THC plasma concentrations. The red shaded areas represent the 5$^{th}$ to 95$^{th}$ percentiles of predicted values. The red lines and blue circles represent the mean predicted value and observed concentrations, respectively.

**Table S1.** PBPK predicted and observed CBD and 7-OH-CBD exposure in healthy adults.

| Formulation | Trial | Model/ Validation[a] | Dose | Observed $AUC_{0-t}$ (h·ng/mL) | Predicted $AUC_{0-t}$ (h·ng/mL) | AUC Predicted: Observed | Observed $C_{max}$ (ng/mL) | Predicted $C_{max}$ (ng/mL) | $C_{max}$ Predicted: Observed |
|---|---|---|---|---|---|---|---|---|---|
| **CBD** | | | | | | | | | |
| IV | Ohlsson 1986[1] | M | 20 mg SD | 278.17 | 295.49 | 1.06 | 686.00 | 967.55 | 1.41 |
| | Meyer 2018[2] | V | 1.6 mg CBD and 1.6 mg THC SD, with Tween 80 | 13.65 | 13.39 | 0.98 | 22.00 | 24.90 | 1.13 |
| Oromucosal spray | Stott 2013a[3] | M | 10 mg CBD and 10.8 mg THC SD, pre-ketoconazole | 1.82 | 2.80 | 1.54 | 0.66 | 0.72 | 1.09 |
| | | M | 10 mg CBD and 10.8 mg THC SD, post-ketoconazole | 4.83 | 5.03 | 1.04 | 1.25 | 1.14 | 0.91 |
| | | M | 10 mg CBD and 10.8 mg THC SD, pre-omeprazole | 1.83 | 2.69 | 1.47 | 0.63 | 0.69 | 1.10 |
| | | M | 10 mg CBD and 10.8 mg THC SD, post-omeprazole | 2.25 | 3.20 | 1.42 | 0.73 | 0.80 | 1.08 |
| | | V | 10 mg CBD and 10.8 mg THC SD, pre-rifampicin | 3.23 | 2.69 | 0.83 | 1.03 | 0.71 | 0.69 |
| | | V | 10 mg CBD and 10.8 mg THC SD, post-rifampicin | 1.31 | 1.34 | 1.02 | 0.50 | 0.43 | 0.86 |
| | Stott 2013b[4] | V | 5 mg SD | 1.54[c] | 1.34[c] | 0.87 | 0.39 | 0.35 | 0.90 |
| | | V | 10 mg SD | 5.02[c] | 2.72[c] | 0.54 | 1.15 | 0.71 | 0.62 |
| | | V | 20 mg SD | 10.37[c] | 5.54[c] | 0.53 | 2.17 | 1.45 | 0.67 |
| Oral solution (Epidiolex) | Taylor 2018[5] | M | 750 mg SD[b] | 1070.00 | 1071.76 | 1.00 | 290.80 | 275.22 | 0.95 |
| | | M | 3000 mg SD[b] | 2669.00 | 2457.51 | 0.92 | 533.00 | 522.13 | 0.98 |
| | | M | 6000 mg SD[b] | 3696.00 | 3767.69 | 1.02 | 782.00 | 801.97 | 1.03 |
| | | V | 1500 mg SD[b] | 1517.00 | 1274.37 | 0.84 | 292.40 | 275.34 | 0.94 |
| | | V | 4500 mg SD[b] | 3216.00 | 2925.67 | 0.91 | 723.10 | 635.50 | 0.88 |
| **7-OH-CBD** | | | | | | | | | |
| Oral solution (Epidiolex) | Taylor 2018[5] | M | 750 mg SD[b] | 699.00 | 846.84 | 1.21 | 123.00 | 209.19 | 1.70 |
| | | M | 3000 mg SD[b] | 1959.00 | 2068.42 | 1.06 | 332.20 | 436.01 | 1.31 |
| | | M | 6000 mg SD[b] | 3299.00 | 3209.71 | 0.97 | 515.80 | 674.68 | 1.31 |
| | | V | 1500 mg SD[b] | 1616.00 | 1050.25 | 0.65 | 238.70 | 220.63 | 0.92 |
| | | V | 4500 mg SD[b] | 2810.00 | 2284.03 | 0.81 | 404.80 | 480.88 | 1.19 |

The observed area under the concentration-time curve from time zero to time of the last observed concentration ($AUC_{0-t}$) and the maximum concentration ($C_{max}$) was presented as the reported mean value. IV, intravenous; SD, single dose.

[a] M, dataset was used for developing model; V, dataset was used for validation.

[b] Geometric mean.

[c] $AUC_{0-24}$.

**Table S2.** PBPK predicted and observed THC exposure in healthy adults.

| Formulation | Trial | Model/ Validation[a] | Dose | Observed $AUC_{0-t}$ (h·ng/mL) | Predicted $AUC_{0-t}$ (h·ng/mL) | AUC Predicted: Observed | Observed $C_{max}$ (ng/mL) | Predicted $C_{max}$ (ng/mL) | $C_{max}$ Predicted: Observed |
|---|---|---|---|---|---|---|---|---|---|
| IV | Hunt 1980[6] | M | 2 mg SD, before chronic THC | 30.39[b] | 32.61 | 1.07 | 126.05 | 133.04 | 1.06 |
| | | M | 2 mg SD, after chronic THC | 24.96[b] | 32.61 | 1.31 | 106.19 | 133.04 | 1.25 |
| | Ohlsson 1982[7] | M | 5 mg SD, heavy users | 86.33 | 88.89 | 1.03 | 60.70 | 43.73 | 0.72 |
| | | M | 5 mg SD, light users | 91.00 | 88.89 | 0.98 | 71.60 | 43.73 | 0.61 |
| | Naef 2004[8] | M | 0.053 mg/kg SD, with Tween 80 | 117.13 | 59.61 | 0.51 | 283.90 | 302.80 | 1.07 |
| | Ohlsson 1980[9] | V | 5 mg SD | 72.17 | 70.54 | 0.98 | 220.00 | 277.37 | 1.26 |
| | Lindgren 1981[10] | V | 5 mg SD, frequent user | 71.67 | 69.89 | 0.98 | 288.00 | 275.91 | 0.96 |
| | | V | 5 mg SD, non-frequent user | 100.67 | 69.89 | 0.69 | 302.00 | 275.91 | 0.91 |
| | Kelly 1992[11] | V | 5 mg SD, frequent user | 165.13 | 97.37 | 0.59 | 437.60 | 728.47 | 1.66 |
| | | V | 5 mg SD, non-frequent user | 118.23 | 97.37 | 0.82 | 386.10 | 728.47 | 1.89 |
| | Morrison 2009[12] | V | 2.5 mg SD | 34.12 | 37.73 | 1.11 | 176.68 | 176.85 | 1.00 |
| | Morrison 2011[13] | V | 1.25 mg SD | 21.42[b] | 15.93 | 0.74 | 109.00 | 95.18 | 0.87 |
| | Barkus 2011[14] | V | 2.5 mg SD | 29.22 | 31.46 | 1.08 | 152.62 | 175.98 | 1.15 |
| | Meyer 2018[2] | V | 1.6 mg SD, with 1.6 mg CBD and Tween 80 | 8.57[b] | 8.82 | 1.03 | 30.00 | 25.43 | 0.85 |
| Oromucosal spray | Stott 2013a[3] | M | 10.8 mg THC and 10 mg CBD SD, pre-ketoconazole | 8.19 | 10.12 | 1.24 | 2.65 | 3.08 | 1.16 |
| | | M | 10.8 mg THC and 10 mg CBD SD, post-ketoconazole | 15.38 | 28.18 | 1.83 | 3.36 | 6.53 | 1.94 |
| | | M | 10.8 mg THC and 10 mg CBD SD, pre-omeprazole | 8.76 | 10.12 | 1.16 | 2.50 | 3.08 | 1.23 |
| | | M | 10.8 mg THC and 10 mg CBD SD, post-omeprazole | 7.41 | 10.14 | 1.37 | 2.48 | 3.09 | 1.25 |
| | | V | 10.8 mg THC and 10 mg CBD SD, pre-rifampicin | 9.10 | 10.12 | 1.11 | 2.94 | 3.08 | 1.05 |
| | | V | 10.8 mg THC and 10 mg CBD SD, post-rifampicin | 6.53 | 5.48 | 0.84 | 1.88 | 2.09 | 1.11 |
| | Stott 2013b[4] | V | 5.4 mg SD | 2.99 | 5.11 | 1.71 | 1.48 | 1.62 | 1.09 |
| | | V | 10.8 mg SD | 11.64 | 10.26 | 0.88 | 3.98 | 3.25 | 0.82 |
| | | V | 21.6 mg SD | 22.70 | 20.67 | 0.91 | 5.40 | 6.42 | 1.19 |
| Inhalation | Ohlsson 1980[9] | / | 13 mg SD | 33.00 | 26.03 | 0.79 | 77.00 | 39.87 | 0.52 |
| | Lindgren 1981[10] | / | 13.4 mg SD, light user | 24.00 | 21.11 | 0.88 | 67.00 | 37.02 | 0.55 |
| | | / | 12.7 mg SD, heavy user, $F_{inh}$ = 0.50 | 36.00 | 43.32 | 1.20 | 98.00 | 76.14 | 0.78 |
| | Barnett 1982[15] | / | 8.94 mg SD | 16.45 | 17.44 | 1.06 | 45.60 | 30.19 | 0.66 |
| | Ohlsson 1982[7] | / | 8.9 mg SD, light user | 24.00 | 30.44 | 1.27 | 16.00 | 26.35 | 1.64 |
| | | / | 8.9 mg SD heavy user | 41.00 | 30.39 | 0.74 | 32.00 | 26.35 | 0.82 |
| | Perez-Reyes 1982[16] | / | 9.7 mg SD, $F_{inh}$ = 0.70 | 68.72 | 61.52 | 0.90 | 94.30 | 78.93 | 0.84 |
| | | / | 12.8 mg SD, $F_{inh}$ = 0.70 | 77.45 | 81.20 | 1.05 | 107.40 | 101.90 | 0.95 |
| | | / | 16 mg SD, $F_{inh}$ = 0.70 | 101.08 | 101.51 | 1.00 | 155.10 | 127.38 | 0.82 |
| | McBurney 1986[17] | / | 0.15 mg/kg SD | 67.00 | 68.88 | 1.03 | 85.00 | 72.78 | 0.86 |
| | Johansson 1988[18] | / | 15 mg SD | 36.00 | 54.15 | 1.51 | 10.00 | 11.09 | 1.11 |
| | Huestis 1992[19] | / | 15.8 mg SD, $F_{inh}$ = 0.35 | 79.00 | 82.47 | 1.04 | 84.00 | 77.18 | 0.92 |

| Formulation | Trial | Model/ Validation[a] | Dose | Observed $AUC_{0-t}$ (h·ng/mL) | Predicted $AUC_{0-t}$ (h·ng/mL) | AUC Predicted: Observed | Observed $C_{max}$ (ng/mL) | Predicted $C_{max}$ (ng/mL) | $C_{max}$ Predicted: Observed |
|---|---|---|---|---|---|---|---|---|---|
| Inhalation | Huestis 1992[19] | / | 33.8 mg SD, $F_{inh}$ = 0.35 | 152.00 | 176.51 | 1.16 | 162.00 | 165.15 | 1.02 |
| | Mattes 1994[20] | / | 2.57 mg SD, $F_{inh}$ = 1 | 24.50 | 21.86 | 0.89 | 9.09 | 8.57 | 0.94 |
| | Naef 2004[8] | / | 0.053 mg/kg SD, $F_{inh}$ = 0.5 | 20.50 | 20.21 | 0.99 | 19.27 | 24.75 | 1.28 |
| | Kauert 2007[21] | / | 0.25 mg/kg SD | 23.00 | 33.71 | 1.47 | 48.00 | 28.73 | 0.60 |
| | | / | 0.5 mg/kg SD | 40.00 | 67.45 | 1.69 | 79.00 | 57.48 | 0.73 |
| | Toennes 2008[22] | / | 0.5 mg/kg SD, chronic user | 86.00 | 94.53 | 1.10 | 120.90 | 115.06 | 0.95 |
| | | / | 0.5 mg/kg SD, occasional user, $F_{inh}$ = 0.10 | 35.00 | 42.60 | 1.22 | 49.10 | 51.80 | 1.05 |
| | Hunault 2008[23] | / | 29.3 mg SD | 76.00 | 72.00 | 0.95 | 135.00 | 84.05 | 0.62 |
| | | / | 49.1 mg SD | 113.00 | 120.43 | 1.07 | 203.00 | 140.77 | 0.69 |
| | | / | 69.4 mg SD | 150.00 | 170.29 | 1.14 | 231.00 | 199.01 | 0.86 |
| | Toennes 2011[24] | / | 0.4 mg/kg SD, chronic user | 88.00 | 64.74 | 0.74 | 112.00 | 91.84 | 0.82 |
| | Hunault 2014[25] | / | 29.3 mg SD | 69.00 | 73.30 | 1.06 | 124.00 | 85.26 | 0.69 |
| | | / | 49.1 mg SD | 102.00 | 122.67 | 1.20 | 168.00 | 142.74 | 0.85 |
| | | / | 69.4 mg SD | 135.00 | 173.45 | 1.28 | 190.00 | 201.79 | 1.06 |
| | Desrosiers 2014[26] | / | 54 mg SD, frequent user | 178.00 | 159.73 | 0.90 | 47.70 | 55.13 | 1.16 |
| | | / | 54 mg SD, occasional user, $F_{inh}$ = 0.05 | 29.10 | 37.02 | 1.28 | 16.70 | 12.77 | 0.76 |
| | Hartman 2015[27] | / | 14.5 mg SD | 44.60 | 35.57 | 0.80 | 46.50 | 45.72 | 0.98 |
| | | / | 33.5 mg SD | 56.20 | 82.23 | 1.46 | 62.10 | 100.6 | 1.62 |
| | Newmeyer 2017[28] | / | 50.6 mg SD, whole blood concentration, occasional user, $F_{inh}$ = 0.08 | / | / | / | 44.00 | 39.95 | 0.91 |
| | | / | 50.6 mg SD, whole blood concentration, frequent user | / | / | / | 117.00 | 104.71 | 0.89 |
| | Meyer 2018[2] | / | 1.6 mg SD, with 1.6mg CBD, $F_{inh}$ = 0.35 | 1.68[b] | 3.16 | 1.88 | 10.00 | 7.73 | 0.77 |
| | Matheson 2020[29] | / | 73.3 mg SD, female, $F_{inh}$ = 0.025 | 11.97 | 18.66 | 1.56 | 21.91 | 26.54 | 1.21 |
| | | / | 86 mg SD, male, $F_{inh}$ = 0.025 | 27.48 | 22.05 | 0.80 | 42.05 | 26.47 | 0.63 |
| Oral | Parikh 2016[30] | M | 4.25 mg SD, replicate 1 | 3.44 | 4.21 | 1.22 | 1.81 | 1.25 | 0.69 |
| | | M | 4.25 mg SD, replicate 2 | 3.62 | 4.21 | 1.16 | 2.08 | 1.25 | 0.60 |
| | Nadulski 2005[31] | V | 10 mg SD | 5.96 | 9.92 | 1.66 | 3.19 | 2.94 | 0.92 |
| | Menetrey 2005[32] | V | 16.5 mg SD, whole blood concentration | 16.25 | 11.46 | 0.71 | 3.72 | 3.41 | 0.92 |
| | | V | 20 mg SD, whole blood concentration | 17.52 | 13.93 | 0.80 | 2.78 | 3.79 | 1.36 |
| | | V | 45.7 mg SD, whole blood concentration | 43.61 | 31.95 | 0.73 | 8.39 | 9.52 | 1.13 |

$AUC_{0-t}$ and $C_{max}$ were presented as the reported mean value unless labeled. IV, intravenous; SD, single dose; /, not applied; $F_{inh}$, fraction of drug absorbed from the inhalation, the default $F_{inh}$ is 0.22.

[a] M: dataset was used for developing the model; V: dataset was used for validation.

[b] $AUC_{0-t}$ was calculated using the trapezoidal method.

**Table S3.** PBPK predicted and observed 11-OH-THC and 11-COOH-THC exposure in healthy adults.

| Formulation | Trial | Model/ Validation[a] | Dose | Observed $AUC_{0-t}$ (h·ng/mL) | Predicted $AUC_{0-t}$ (h·ng/mL) | AUC Predicted: Observed | Observed $C_{max}$ (ng/mL) | Predicted $C_{max}$ (ng/mL) | $C_{max}$ Predicted: Observed |
|---|---|---|---|---|---|---|---|---|---|
| **11-OH-THC** | | | | | | | | | |
| IV | Naef 2004[8] | M | 0.053 mg/kg IV Single dose | 13.70[b] | 7.35 | 0.54 | 9.18 | 7.17 | 0.78 |
| | Meyer 2018[2] | V | 1.6 mg SD, with 1.6 mg CBD and Tween 80 | 4.50[b] | 2.32 | 0.52 | 5.00 | 3.25 | 0.65 |
| Oromucosal spray | Stott 2013a[3] | M | 10.8 mg THC and 10 mg CBD SD, pre-ketoconazole | 21.78 | 15.90 | 0.73 | 3.59 | 2.97 | 0.83 |
| | | M | 10.8 mg THC and 10 mg CBD SD, post-ketoconazole | 84.34 | 82.53 | 0.98 | 10.92 | 11.93 | 1.09 |
| | | M | 10.8 mg THC and 10 mg CBD SD, pre-omeprazole | 21.52 | 15.90 | 0.74 | 3.48 | 2.97 | 0.85 |
| | | M | 10.8 mg THC and 10 mg CBD SD, post-omeprazole | 17.69 | 16.19 | 0.92 | 2.84 | 2.97 | 1.05 |
| | | V | 10.8 mg THC and 10 mg CBD SD, pre-rifampicin | 18.61 | 15.90 | 0.85 | 3.38 | 2.97 | 0.88 |
| | | V | 10.8 mg THC and 10 mg CBD SD, post-rifampicin | 1.84 | 2.82 | 1.53 | 0.45 | 0.69 | 1.53 |
| | Stott 2013b[4] | V | 5.4 mg SD | 10.25 | 6.65 | 0.65 | 2.28 | 1.37 | 0.6 |
| | | V | 10.8 mg SD | 28.72 | 14.67 | 0.51 | 4.67 | 2.97 | 0.61 |
| | | V | 21.6 mg SD | 60.70 | 37.49 | 0.62 | 8.28 | 5.82 | 0.70 |
| Inhalation | Huestis 1992[19] | / | 15.8 mg SD, $F_{inh}$ = 0.35 | 8.80 | 15.71 | 1.79 | 5.73 | 6.90 | 1.20 |
| | | / | 33.8 mg SD, $F_{inh}$ = 0.35 | 17.05 | 33.82 | 1.98 | 7.23 | 14.93 | 2.06 |
| | Naef 2004[8] | / | 0.053 mg/kg SD, $F_{inh}$ = 0.5 | 4.54[b] | 3.64 | 0.80 | 1.36 | 2.36 | 1.74 |
| | Kauert 2007[21] | / | 0.25 mg/kg SD | 4.60 | 7.22 | 1.57 | 2.50 | 4.07 | 1.63 |
| | | / | 0.5 mg/kg SD | 8.00 | 14.50 | 1.81 | 3.60 | 8.21 | 2.28 |
| | Toennes 2008[22] | / | 0.5 mg/kg SD, chronic user | 31.00 | 18.00 | 0.58 | 12.30 | 11.04 | 0.90 |
| | | / | 0.5 mg/kg SD, occasional user | 14.00 | 8.76 | 0.63 | 6.70 | 5.47 | 0.82 |
| | Hunault 2008[23] | / | 29.3 mg SD | 24.20 | 13.01 | 0.54 | 9.20 | 7.87 | 0.86 |
| | | / | 49.1 mg SD | 36.70 | 21.93 | 0.60 | 16.40 | 13.3 | 0.81 |
| | | / | 69.4 mg SD | 40.40 | 31.10 | 0.77 | 15.80 | 18.9 | 1.20 |
| | Desrosiers 2014[26] | / | 54 mg SD, frequent user | 22.90 | 33.84 | 1.48 | 10.80 | 9.15 | 0.85 |
| | | / | 54 mg SD, occational user, $F_{inh}$ = 0.05 | 11.40 | 8.99 | 0.79 | 5.30 | 3.84 | 0.72 |
| | Hartman 2015[27] | / | 14.5 mg SD | 5.80 | 7.04 | 1.21 | 4.10 | 4.51 | 1.10 |
| | | / | 33.5 mg SD | 9.80 | 16.34 | 1.67 | 7.00 | 10.01 | 1.43 |
| | Newmeyer 2017[28] | / | 50.6 mg SD, blood concentration, $F_{inh}$ = 0.08, occasional user | / | / | / | 1.90 | 3.79 | 1.99 |
| | | / | 50.6 mg SD, blood concentration frequent user | / | / | / | 7.20 | 9.41 | 1.31 |
| | Meyer 2018[2] | / | 1.6 mg SD, with CBD, $F_{inh}$ = 0.35 | 0.40[b] | 0.64 | 1.60 | 1.00 | 0.76 | 0.76 |
| | Matheson 2020[29] | / | 73.3 mg SD, Female | 3.14 | 5.34 | 1.70 | 2.36 | 3.34 | 1.42 |
| | | / | 86 mg SD, Male | 6.40 | 5.71 | 0.89 | 3.94 | 2.99 | 0.76 |

| Formulation | Trial | Model/ Validation[a] | Dose | Observed $AUC_{0-t}$ (h·ng/mL) | Predicted $AUC_{0-t}$ (h·ng/mL) | AUC Predicted: Observed | Observed $C_{max}$ (ng/mL) | Predicted $C_{max}$ (ng/mL) | $C_{max}$ Predicted: Observed |
|---|---|---|---|---|---|---|---|---|---|
| **11-COOH-THC** | | | | | | | | | |
| IV | Naef 2004[8] | M | 0.053 mg/kg SD | 210.18 | 219.08 | 1.04 | 37.41 | 35.64 | 0.95 |
| | Meyer 2018[2] | V | 1.6 mg SD, with 1.6 mg CBD and Tween 80 | 104.22[b] | 49.96 | 0.48 | 34.00 | 15.90 | 0.47 |
| Inhalation | Perez-Reyes 1982[16] | / | 9.7 mg SD, $F_{inh}$ = 0.70 | 103.90 | 117.57 | 1.13 | 31.50 | 38.67 | 1.23 |
| | | / | 12.8 mg SD, $F_{inh}$ = 0.70 | 130.07 | 154.46 | 1.19 | 43.10 | 50.68 | 1.18 |
| | | / | 16 mg SD, $F_{inh}$ = 0.70 | 145.46 | 192.21 | 1.32 | 45.30 | 62.91 | 1.38 |
| | Huestis 1992[19] | / | 15.8 mg SD, $F_{inh}$ = 0.35 | 446.76 | 237.17 | 0.53 | 20.67 | 35.77 | 1.73 |
| | | / | 33.8 mg SD, $F_{inh}$ = 0.35 | 1190.47 | 500.23 | 0.42 | 50.60 | 74.55 | 1.47 |
| | Mattes 1994[20] | / | 2.57 mg SD, $F_{inh}$ = 1 | 103.24[b] | 53.78 | 0.52 | 18.93 | 13.49 | 0.71 |
| | Naef 2004[8] | / | 0.053 mg/kg SD, $F_{inh}$ = 0.5 | 61.43[b] | 46.51 | 0.76 | 9.80 | 12.53 | 1.28 |
| | Hunault 2008[23] | / | 29.3 mg SD | 90.20 | 164.90 | 1.83 | 30.40 | 41.75 | 1.37 |
| | | / | 49.1 mg SD | 149.70 | 273.41 | 1.83 | 46.20 | 69.67 | 1.51 |
| | | / | 69.4 mg SD | 160.90 | 382.48 | 2.37 | 90.20 | 92.82 | 1.03 |
| | Desrosiers 2014[26] | / | 54 mg SD, frequent user | 691.00 | 519.71 | 0.75 | 96.50 | 82.48 | 0.85 |
| | | / | 54 mg SD, occational user, $F_{inh}$ = 0.05 | 140.00 | 143.99 | 1.16 | 18.60 | 21.84 | 1.17 |
| | Hartman 2015[27] | / | 14.5 mg SD | 97.30 | 83.85 | 0.86 | 25.30 | 22.54 | 0.89 |
| | | / | 33.5 mg SD | 134.00 | 191.51 | 1.43 | 38.10 | 51.09 | 1.34 |
| | Meyer 2018[2] | / | 1.6 mg SD, with 1.6 mg CBD, $F_{inh}$ = 0.35 | 17.66[b] | 9.37 | 0.53 | 6.00 | 4.07 | 0.68 |
| | Matheson 2020[29] | / | 73.3 mg SD, Female | 38.85 | 58.75 | 1.51 | 11.70 | 17.87 | 1.53 |
| | | / | 86 mg SD, Male | 86.05 | 69.97 | 0.81 | 25.47 | 18.95 | 0.74 |

$AUC_{0-t}$ and $C_{max}$ were presented as the reported mean value unless labeled. IV, intravenous; SD, single dose; /, not applied; $F_{inh}$, fraction of drug absorbed from the inhalation, the default $F_{inh}$ is 0.22.

[a] M: dataset was used for developing the model; V: dataset was used for validation.

[b] $AUC_{0-t}$ was calculated using the trapezoidal method.

**Supplemental References**


1. Ohlsson A, Lindgren JE, Andersson S, et al. Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration. *Biomed Environ Mass Spectrom*. Feb 1986;13(2):77-83. doi:10.1002/bms.1200130206
2. Meyer P, Langos M, Brenneisen R. Human Pharmacokinetics and Adverse Effects of Pulmonary and Intravenous THC-CBD Formulations. *Med Cannabis Cannabinoids*. Jun 2018;1(1):36-43. doi:10.1159/000489034
3. Stott C, White L, Wright S, Wilbraham D, Guy G. A Phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of Rifampicin, Ketoconazole, and Omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers. *Springerplus*. Dec 2013;2(1):236. doi:10.1186/2193-1801-2-236
4. Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray. *Eur J Clin Pharmacol*. May 2013;69(5):1135-47. doi:10.1007/s00228-012-1441-0
5. Taylor L, Gidal B, Blakey G, Tayo B, Morrison G. A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects. *CNS Drugs*. Nov 2018;32(11):1053-1067. doi:10.1007/s40263-018-0578-5
6. Hunt CA, Jones RT. Tolerance and disposition of tetrahydrocannabinol in man. *J Pharmacol Exp Ther*. Oct 1980;215(1):35-44.
7. Ohlsson A, Lindgren JE, Wahlen A, et al. Single dose kinetics of deuterium labelled delta 1-tetrahydrocannabinol in heavy and light cannabis users. *Biomed Mass Spectrom*. Jan 1982;9(1):6-10. doi:10.1002/bms.1200090103
8. Naef M, Russmann S, Petersen-Felix S, Brenneisen R. Development and pharmacokinetic characterization of pulmonal and intravenous delta-9-tetrahydrocannabinol (THC) in humans. *J Pharm Sci*. May 2004;93(5):1176-84. doi:10.1002/jps.20037
9. Ohlsson A, Lindgren JE, Wahlen A, et al. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clin Pharmacol Ther*. Sep 1980;28(3):409-16. doi:10.1038/clpt.1980.181
10. Lindgren JE, Ohlsson A, Agurell S, Hollister L, Gillespie H. Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. *Psychopharmacology (Berl)*. 1981;74(3):208-12. doi:10.1007/BF00427095
11. Kelly P, Jones RT. Metabolism of tetrahydrocannabinol in frequent and infrequent marijuana users. *J Anal Toxicol*. Jul-Aug 1992;16(4):228-35. doi:10.1093/jat/16.4.228
12. Morrison PD, Zois V, McKeown DA, et al. The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. *Psychol Med*. Oct 2009;39(10):1607-16. doi:10.1017/S0033291709005522
13. Morrison PD, Nottage J, Stone JM, et al. Disruption of frontal theta coherence by Delta9-tetrahydrocannabinol is associated with positive psychotic symptoms. *Neuropsychopharmacology*. Mar 2011;36(4):827-36. doi:10.1038/npp.2010.222
14. Barkus E, Morrison PD, Vuletic D, et al. Does intravenous Delta9-tetrahydrocannabinol increase dopamine release? A SPET study. *J Psychopharmacol*. Nov 2011;25(11):1462-8. doi:10.1177/0269881110382465
15. Barnett G, Chiang CW, Perez-Reyes M, Owens SM. Kinetic study of smoking marijuana. *J Pharmacokinet Biopharm*. Oct 1982;10(5):495-506. doi:10.1007/BF01059033
16. Perez-Reyes M, Di Guiseppi S, Davis KH, Schindler VH, Cook CE. Comparison of effects of marihuana cigarettes to three different potencies. *Clin Pharmacol Ther*. May 1982;31(5):617-24. doi:10.1038/clpt.1982.86

17. McBurney LJ, Bobbie BA, Sepp LA. GC/MS and EMIT analyses for delta 9-tetrahydrocannabinol metabolites in plasma and urine of human subjects. *J Anal Toxicol*. Mar-Apr 1986;10(2):56-64. doi:10.1093/jat/10.2.56
18. Johansson E, Agurell S, Hollister LE, Halldin MM. Prolonged apparent half-life of delta 1-tetrahydrocannabinol in plasma of chronic marijuana users. *J Pharm Pharmacol*. May 1988;40(5):374-5. doi:10.1111/j.2042-7158.1988.tb05272.x
19. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. *J Anal Toxicol*. Sep-Oct 1992;16(5):276-82. doi:10.1093/jat/16.5.276
20. Mattes RD, Engelman K, Shaw LM, Elsohly MA. Cannabinoids and appetite stimulation. *Pharmacol Biochem Behav*. Sep 1994;49(1):187-95. doi:10.1016/0091-3057(94)90475-8
21. Kauert GF, Ramaekers JG, Schneider E, Moeller MR, Toennes SW. Pharmacokinetic properties of delta9-tetrahydrocannabinol in serum and oral fluid. *J Anal Toxicol*. Jun 2007;31(5):288-93. doi:10.1093/jat/31.5.288
22. Toennes SW, Ramaekers JG, Theunissen EL, Moeller MR, Kauert GF. Comparison of cannabinoid pharmacokinetic properties in occasional and heavy users smoking a marijuana or placebo joint. *J Anal Toxicol*. Sep 2008;32(7):470-7. doi:10.1093/jat/32.7.470
23. Hunault CC, Mensinga TT, de Vries I, et al. Delta-9-tetrahydrocannabinol (THC) serum concentrations and pharmacological effects in males after smoking a combination of tobacco and cannabis containing up to 69 mg THC. *Psychopharmacology (Berl)*. Dec 2008;201(2):171-81. doi:10.1007/s00213-008-1260-2
24. Toennes SW, Schneider K, Kauert GF, et al. Influence of ethanol on cannabinoid pharmacokinetic parameters in chronic users. *Anal Bioanal Chem*. Apr 2011;400(1):145-52. doi:10.1007/s00216-010-4449-2
25. Hunault CC, Bocker KB, Stellato RK, et al. Acute subjective effects after smoking joints containing up to 69 mg Delta9-tetrahydrocannabinol in recreational users: a randomized, crossover clinical trial. *Psychopharmacology (Berl)*. Dec 2014;231(24):4723-33. doi:10.1007/s00213-014-3630-2
26. Desrosiers NA, Himes SK, Scheidweiler KB, et al. Phase I and II cannabinoid disposition in blood and plasma of occasional and frequent smokers following controlled smoked cannabis. *Clin Chem*. Apr 2014;60(4):631-43. doi:10.1373/clinchem.2013.216507
27. Hartman RL, Brown TL, Milavetz G, et al. Controlled Cannabis Vaporizer Administration: Blood and Plasma Cannabinoids with and without Alcohol. *Clin Chem*. Jun 2015;61(6):850-69. doi:10.1373/clinchem.2015.238287
28. Newmeyer MN, Swortwood MJ, Andersson M, et al. Cannabis Edibles: Blood and Oral Fluid Cannabinoid Pharmacokinetics and Evaluation of Oral Fluid Screening Devices for Predicting Delta(9)-Tetrahydrocannabinol in Blood and Oral Fluid following Cannabis Brownie Administration. *Clin Chem*. Mar 2017;63(3):647-662. doi:10.1373/clinchem.2016.265371
29. Matheson J, Sproule B, Di Ciano P, et al. Sex differences in the acute effects of smoked cannabis: evidence from a human laboratory study of young adults. *Psychopharmacology (Berl)*. Feb 2020;237(2):305-316. doi:10.1007/s00213-019-05369-y
30. Parikh N, Kramer WG, Khurana V, Cognata Smith C, Vetticaden S. Bioavailability study of dronabinol oral solution versus dronabinol capsules in healthy volunteers. *Clin Pharmacol*. 2016;8:155-162. doi:10.2147/CPAA.S115679
31. Nadulski T, Pragst F, Weinberg G, et al. Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of Delta9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract. *Ther Drug Monit*. Dec 2005;27(6):799-810. doi:10.1097/01.ftd.0000177223.19294.5c

32. Menetrey A, Augsburger M, Favrat B, et al. Assessment of driving capability through the use of clinical and psychomotor tests in relation to blood cannabinoids levels following oral administration of 20 mg dronabinol or of a cannabis decoction made with 20 or 60 mg Delta9-THC. *J Anal Toxicol*. Jul-Aug 2005;29(5):327-38. doi:10.1093/jat/29.5.327