

## TK NTP Study K01090C Resveratrol

Sex/Species: male and female Harlan Sprague Dawley rats; male and female B6C3F1/N mice

Vehicles: intravenous, Cremophor EL:ethanol:saline (1:1:8) (v:v:v); oral, 0.5% methylcellulose in water.

CASRN 501-36-0

Analytes: test article trans-Resveratrol (RES) and metabolites trans-Resveratrol 3-sulfate sodium salt (R3S) and trans-Resveratrol 3-O- $\beta$ -D-glucuronide (R3G)

### Studies Performed:

- Single intravenous dose of 10 mg/kg to male and female rats. (n = 3 plasma samples per time point)
- Single oral gavage dose of 312.5, 625, or 1250 mg/kg to male and female rats (n = 3 plasma samples per time point)
- Single intravenous dose of 10 mg/kg to male and female mice. (n = 3 plasma samples per time point)
- Single oral gavage dose of 625, 1250, or 2500 mg/kg to male and female rats (n = 3 plasma samples per time point)

The parameters were estimated using WinNonlin, Version 7.0 (Pharsight Corporation) software compartmental models. Samples were collected at pre-dose to 13-14 (rats) or 11-12 (mice) time points post-administration. The average of the three sample concentrations per time point were used for modeling.

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**Table 1. RES Plasma TK Parameters for Harlan Sprague Dawley Rats following a Single IV Administration of RES to Males and Females (10 mg/kg)<sup>a,b</sup>**

<b>Parameter</b>	<b>Males</b>	<b>Females</b>
Cmax_obs (ng/mL) <sup>c</sup>	5960	3870
Cmax_pred (ng/mL) <sup>d</sup>	11600 ± 7500	5560 ± 4080
Alpha_Half-life (min)	3.83 ± 1.31	4.85 ± 2.04
Beta_Half-life (min)	95.3 ± 9.3	78.3 ± 13.2
K10 (min <sup>-1</sup> )	0.112 ± 0.048	0.0954 ± 0.0454
K10_Half-life (min)	6.21 ± 2.64	7.26 ± 3.45
K12 (min <sup>-1</sup> )	0.0649 ± 0.0234	0.0431 ± 0.0223
K21 (min <sup>-1</sup> )	0.0118 ± 0.0023	0.0133 ± 0.0036
AUC_0-T (ng/mL·min) <sup>c</sup>	128000	79400
AUCinf_pred (predicted) (ng/mL·min)	104000 ± 27000	58300 ± 18200
Cl (mL/min/kg)	96.2 ± 24.6	172 ± 53
Cl2 (mL/min/kg)	56.0 ± 34.0	77.4 ± 55.5
MRT (min)	58.2 ± 14.5	44.5 ± 13.6
V1 (mL/kg)	862 ± 556	1800 ± 1320
V2 (mL/kg)	4740 ± 2210	5840 ± 3350

- a. Based on a two-compartment model with bolus input, first order output, and 1/Yhat<sup>2</sup> weighting.
- b. Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- c. Observed values do not have a reported SEM.
- d. Cmax\_pred based on the model prediction at 0 minutes.

**Table 2. RES Plasma TK Parameters for Male Harlan Sprague Dawley Rats following a Single Gavage Administration of RES<sup>a,b</sup>**

<b>Parameter</b>	<b>312.5 mg/kg</b>	<b>625 mg/kg</b>	<b>1250 mg/kg</b>
Cmax_obs (ng/mL) <sup>c</sup>	820	1140	2650
Cmax_pred (ng/mL)	902 ± 187	1170 ± 290	1450 ± 360
Tmax_obs (min) <sup>c</sup>	90.0	180	480
Tmax_pred (min)	58.9 ± 23.3	97.5 ± 36.2	182 ± 56
K01 (min <sup>-1</sup> )	0.0589 ± 0.0343	0.0304 ± 0.0186	0.0207 ± 0.0114
K01_Half-life (min)	11.8 ± 6.8	22.8 ± 14.0	33.4 ± 18.4
K10 (min <sup>-1</sup> )	0.00207 ± 0.00058	0.00189 ± 0.00074	0.000520 ± 0.000680
K10_Half-life (min)	334 ± 93	366 ± 143	1330 ± 1740
AUC <sub>0-T</sub> (ng/mL·min) <sup>c</sup>	386000	518000	1330000
AUC <sub>inf_pred</sub> (ng/mL·min)	491000 ± 97000	745000 ± 185000	3080000 ± 3220000
Cl <sub>F</sub> (mL/min/kg)	636 ± 126	839 ± 209	406 ± 426
V <sub>F</sub> (mL/kg)	307000 ± 79000	443000 ± 152000	782000 ± 272000
Bioavailability (%)	15.1	11.5	23.7

- a. Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- b. Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- c. Observed values do not have a reported SEM.

**Table 3. RES Plasma TK Parameters for Female Harlan Sprague Dawley Rats following a Single Gavage Administration of RES<sup>a,b</sup>**

<b>Parameter</b>	<b>312.5 mg/kg</b>	<b>625 mg/kg</b>	<b>1250 mg/kg</b>
Cmax_obs (ng/mL) <sup>c</sup>	420	785	1530
Cmax_pred (ng/mL)	493 ± 122	723 ± 149	1230 ± 250
Tmax_obs (min) <sup>c</sup>	240	480	360
Tmax_pred (min)	49.9 ± 27.4	46.0 ± 22.2	263 ± 55
K01 (min <sup>-1</sup> )	0.0835 ± 0.0637	0.0924 ± 0.0611	0.0115 ± 0.0055
K01_Half-life (min)	8.30 ± 6.33	7.50 ± 4.96	60.0 ± 28.6
K10 (min <sup>-1</sup> )	0.00138 ± 0.00066	0.00140 ± 0.00055	0.000656 ± 0.000654
K10_Half-life (min)	502 ± 238	495 ± 192	1060 ± 1050
AUC <sub>0-T</sub> (ng/mL·min) <sup>c</sup>	288000	473000	1010000
AUC <sub>inf_pred</sub> (ng/mL·min)	382000 ± 130000	551000 ± 154000	2230000 ± 1600000
Cl <sub>F</sub> (mL/min/kg)	817 ± 277	1140 ± 320	561 ± 402
V <sub>F</sub> (mL/kg)	592000 ± 171000	810000 ± 193000	855000 ± 299000
Bioavailability (%)	21.0	15.1	30.6

- Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- Observed values do not have a reported SEM.

**Table 4. RES Plasma TK Parameters for B6C3F1/N Mice following a Single IV Administration of RES to Males and Females (10 mg/kg)<sup>a,b</sup>**

<b>Parameter</b>	<b>Males</b>	<b>Females</b>
Cmax_obs (ng/mL) <sup>c</sup>	3330	3770
Cmax_pred (ng/mL) <sup>d</sup>	4410 ± 4970	4420 ± 1090
Alpha_Half-life (min)	7.23 ± 40.5	14.3 ± 7.3
Beta_Half-life (min)	37.3 ± 7.1	40.5 ± 9.2
K10 (min <sup>-1</sup> )	0.0238 ± 0.0254	0.0320 ± 0.0065
K10_Half-life (min)	29.1 ± 31.0	21.7 ± 4.4
K12 (min <sup>-1</sup> )	0.0158 ± 0.161	0.00759 ± 0.00878
K21 (min <sup>-1</sup> )	0.0749 ± 0.364	0.0259 ± 0.0147
AUC_0-T (ng/mL·min) <sup>c</sup>	157000	140000
AUCinf_pred (predicted) (ng/mL·min)	185000 ± 34000	138000 ± 13000
Cl (mL/min/kg)	54.0 ± 9.7	72.3 ± 6.9
Cl2 (mL/min/kg)	35.8 ± 328	17.2 ± 17.1
MRT (min)	50.8 ± 7.1	40.5 ± 3.3
V1 (mL/kg)	2270 ± 2550	2260 ± 560
V2 (mL/kg)	477 ± 2280	663 ± 346

- a. Based on a two-compartment model with bolus input, first order output, and 1/Yhat<sup>2</sup> weighting.
- b. Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- c. Observed values do not have a reported SEM.
- d. Cmax\_pred based on the model prediction at 0 minutes.

**Table 5. RES Plasma TK Parameters for Male B6C3F1/N Mice following a Single Gavage Administration of RES<sup>a,b</sup>**

<b>Parameter</b>	<b>625 mg/kg</b>	<b>1250 mg/kg</b>	<b>2500 mg/kg</b>
Cmax_obs (ng/mL) <sup>c</sup>	1080	1190	2070
Cmax_pred (ng/mL)	1320 ± 630	1850 ± 770	1890 ± 530
Tmax_obs (min) <sup>c</sup>	5.00	480	120
Tmax_pred (min)	60.8 ± 45.8	101 ± 51	121 ± 40
K01 (min <sup>-1</sup> )	0.00452 ± 0.00225	0.0172 ± 0.0202	0.0237 ± 0.0159
K01_Half-life (min)	153 ± 76	40.4 ± 47.6	29.3 ± 19.6
K10 (min <sup>-1</sup> )	0.0406 ± 0.0519	0.00507 ± 0.00314	0.00163 ± 0.00124
K10_Half-life (min)	17.1 ± 21.8	137 ± 84	424 ± 321
AUC_0-T (ng/mL·min) <sup>c</sup>	376000	513000	854000
AUCinf_pred (ng/mL·min)	384000 ± 163000	607000 ± 242000	1410000 ± 620000
Cl <sub>F</sub> (mL/min/kg)	1630 ± 690	2060 ± 820	1780 ± 780
V <sub>F</sub> (mL/kg)	40000 ± 45000	406000 ± 348000	1090000 ± 480000
Bioavailability (%)	3.32	2.62	3.05

- a. Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- b. Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- c. Observed values do not have a reported SEM.

**Table 6. RES Plasma TK Parameters for Female B6C3F1/N Mice following a Single Gavage Administration of RES<sup>a,b</sup>**

<b>Parameter</b>	<b>625 mg/kg</b>	<b>1250 mg/kg</b>	<b>2500 mg/kg</b>
Cmax_obs (ng/mL) <sup>c</sup>	1110	1480	2630
Cmax_pred (ng/mL)	1040 ± 280	1020 ± 420	1820 ± 440
Tmax_obs (min) <sup>c</sup>	120	360	360
Tmax_pred (min)	36.1 ± 21.7	69.2 ± 48.1	174 ± 45
K01 (min <sup>-1</sup> )	0.0979 ± 0.0842	0.0589 ± 0.0637	0.00593 ± 0.0717
K01_Half-life (min)	7.08 ± 6.08	11.8 ± 12.7	117 ± 1410
K10 (min <sup>-1</sup> )	0.00319 ± 0.00105	0.00108 ± 0.00154	0.00558 ± 0.0664
K10_Half-life (min)	217 ± 72	642 ± 915	124 ± 1480
AUC_0-T (ng/mL·min) <sup>c</sup>	407000	520000	824000
AUCinf_pred (ng/mL·min)	366000 ± 88000	1010000 ± 1090000	860000 ± 187000
Cl1_F (mL/min/kg)	1710 ± 410	1230 ± 1330	2910 ± 630
V1_F (mL/kg)	535000 ± 176000	1140000 ± 600000	521000 ± 6210000
Bioavailability (%)	4.24	5.86	2.49

- a. Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- b. Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- c. Observed values do not have a reported SEM.

**Table 7. R3S Plasma TK Parameters for Harlan Sprague Dawley Rats following a Single IV Administration of RES to Males and Females (10 mg/kg)<sup>a,b</sup>**

<b>Parameter</b>	<b>Males</b>	<b>Females</b>
Cmax_obs (ng/mL) <sup>c</sup>	9500	21000
Cmax_pred (ng/mL) <sup>d</sup>	10400 ± 3800	28000 ± 15900
Alpha_Half-life (min)	8.03 ± 2.33	5.84 ± 2.05
Beta_Half-life (min)	87.4 ± 6.6	79.2 ± 7.4
K10 (min <sup>-1</sup> )	0.0482 ± 0.0134	0.0778 ± 0.0296
K10_Half-life (min)	14.4 ± 4.0	8.91 ± 3.39
K12 (min <sup>-1</sup> )	0.0318 ± 0.0131	0.0363 ± 0.0167
K21 (min <sup>-1</sup> )	0.0142 ± 0.0026	0.0134 ± 0.0026
AUC_0-T (ng/mL·min) <sup>c</sup>	260000	436000
AUCinf_pred (predicted) (ng/mL·min)	216000 ± 28000	360000 ± 85000
MRT (min)	67.2 ± 8.3	47.8 ± 10.6

- a. Based on a two-compartment model with bolus input, first order output, and 1/Yhat<sup>2</sup> weighting.
- b. Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- c. Observed values do not have a reported SEM.
- d. Cmax\_pred based on the model prediction at 0 minutes.



**Table 8. R3S Plasma TK Parameters for Male Harlan Sprague Dawley Rats following a Single Gavage Administration of RES<sup>a,b</sup>**

Parameter	312.5 mg/kg	625 mg/kg	1250 mg/kg
Cmax_obs (ng/mL) <sup>c</sup>	4530	9690	29200
Cmax_pred (ng/mL)	4860 ± 1270	6040 ± 1310	15600 ± 3700
Tmax_obs (min) <sup>c</sup>	180	180	480
Tmax_pred (min)	194 ± 55	245 ± 55	431 ± 80
K10 (min <sup>-1</sup> )	0.00582 ± 0.0130	0.00205 ± 0.00132	0.00198 ± 0.00974
K10_Half-life (min)	119 ± 265	337 ± 217	351 ± 1730
AUC_0-T (ng/mL·min) <sup>c</sup>	2820000	4860000	13800000
AUCinf_pred (ng/mL·min)	2580000 ± 700000	4870000 ± 1100000	18500000 ± 10300000

- Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- Observed values do not have a reported SEM.

**Table 9. R3S Plasma TK Parameters for Female Harlan Sprague Dawley Rats following a Single Gavage Administration of RES<sup>a,b</sup>**

Parameter	312.5 mg/kg	625 mg/kg	1250 mg/kg
Cmax_obs (ng/mL) <sup>c</sup>	9830	15700	24200
Cmax_pred (ng/mL)	6960 ± 2390	12200 ± 2800	17300 ± 4800
Tmax_obs (min) <sup>c</sup>	90.0	240	360
Tmax_pred (min)	183 ± 72	260 ± 59	392 ± 99
K10 (min <sup>-1</sup> )	0.00139 ± 0.00117	0.00105 ± 0.00087	0.000845 ± 0.00142
K10_Half-life (min)	500 ± 423	659 ± 542	820 ± 1380
AUC_0-T (ng/mL·min) <sup>c</sup>	4320000	8370000	16700000
AUCinf_pred (ng/mL·min)	6470000 ± 3030000	15200000 ± 7200000	28400000 ± 27900000

- Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- Parameter estimates are reported to three significant figures.
- Observed values do not have a reported SEM.

**Table 10. R3S Plasma TK Parameters for B6C3F1/N Mice following a Single IV Administration of RES to Males and Females (10 mg/kg)<sup>a,b</sup>**

<b>Parameter</b>	<b>Males</b>	<b>Females</b>
Cmax_obs (ng/mL) <sup>c</sup>	1590	4910
Cmax_pred (ng/mL) <sup>d</sup>	3210 ± 8500	216000 ± 1320000
Alpha_Half-life (min)	2.32 ± 4.99	0.847 ± 1.26
Beta_Half-life (min)	72.3 ± 5.9	59.1 ± 3.8
K10 (min <sup>-1</sup> )	0.0305 ± 0.0764	0.602 ± 1.62
K10_Half-life (min)	22.7 ± 56.9	1.15 ± 3.10
K12 (min <sup>-1</sup> )	0.184 ± 0.596	0.212 ± 0.385
K21 (min <sup>-1</sup> )	0.0940 ± 0.0659	0.0159 ± 0.0189
AUC_0-T (ng/mL·min) <sup>c</sup>	110000	204000
AUCinf_pred (predicted) (ng/mL·min)	105000 ± 18000	359000 ± 1220000
MRT (min)	97.0 ± 14.8	23.8 ± 77.7

- a. Based on a two-compartment model with bolus input, first order output, and 1/Yhat<sup>2</sup> weighting.
- b. Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- c. Observed values do not have a reported SEM.
- d. Cmax\_pred based on the model prediction at 0 minutes.

**Table 11. R3S Plasma TK Parameters for Male B6C3F1/N Mice following a Single Gavage Administration of RES<sup>a,b</sup>**

Parameter	625 mg/kg	1250 mg/kg	2500 mg/kg
Cmax_obs (ng/mL) <sup>c</sup>	3460	3750	5750
Cmax_pred (ng/mL)	9660 ± 2560	5250 ± 1570	6470 ± 1020
Tmax_obs (min) <sup>c</sup>	90.0	60.0	60.0
Tmax_pred (min)	101 ± 30	108 ± 40	156 ± 28
K10 (min <sup>-1</sup> )	0.00724 ± 0.00392	0.00381 ± 0.00187	0.00633 ± 0.0873
K10_Half-life (min)	95.7 ± 51.8	182 ± 89	110 ± 1510
AUC_0-T (ng/mL·min) <sup>c</sup>	1410000	1810000	2630000
AUCinf_pred (ng/mL·min)	2770000 ± 790000	2080000 ± 540000	2740000 ± 420000

- Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- Observed values do not have a reported SEM.

**Table 12. R3S Plasma TK Parameters for Female B6C3F1/N Mice following a Single Gavage Administration of RES<sup>a,b</sup>**

Parameter	625 mg/kg	1250 mg/kg	2500 mg/kg
Cmax_obs (ng/mL) <sup>c</sup>	7400	9070	12000
Cmax_pred (ng/mL)	9160 ± 2230	9560 ± 3190	9770 ± 1860
Tmax_obs (min) <sup>c</sup>	120	360	120
Tmax_pred (min)	55.6 ± 22.8	123 ± 48	150 ± 31
K10 (min <sup>-1</sup> )	0.00391 ± 0.00107	0.00347 ± 0.00223	0.00617 ± 0.0184
K10_Half-life (min)	177 ± 48	200 ± 128	112 ± 335
AUC_0-T (ng/mL·min) <sup>c</sup>	2930000	3160000	4020000
AUCinf_pred (ng/mL·min)	2910000 ± 610000	4220000 ± 1220000	4000000 ± 720000

- Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- Observed values do not have a reported SEM.

**Table 13. R3G Plasma TK Parameters for Harlan Sprague Dawley Rats following a Single IV Administration of RES to Males and Females (10 mg/kg)<sup>a,b</sup>**

<b>Parameter</b>	<b>Males</b>	<b>Females</b>
Cmax_obs (ng/mL) <sup>c</sup>	23800	33300
Cmax_pred (ng/mL) <sup>d</sup>	26400 ± 13200	57000 ± 29600
Alpha_Half-life (min)	9.31 ± 6.56	7.62 ± 3.28
Beta_Half-life (min)	67.2 ± 4.7	159 ± 29
K10 (min <sup>-1</sup> )	0.0280 ± 0.0125	0.0346 ± 0.0151
K10_Half-life (min)	24.7 ± 11.0	20.0 ± 8.8
K12 (min <sup>-1</sup> )	0.0293 ± 0.0324	0.0493 ± 0.0256
K21 (min <sup>-1</sup> )	0.0274 ± 0.0125	0.0115 ± 0.0038
AUC_0-T (ng/mL·min) <sup>c</sup>	872000	1410000
AUCinf_pred (predicted) (ng/mL·min)	941000 ± 125000	1650000 ± 240000
MRT (min)	73.9 ± 8.2	153 ± 29

- a. Based on a two-compartment model with bolus input, first order output, and 1/Yhat<sup>2</sup> weighting.
- b. Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- c. Observed values do not have a reported SEM.
- d. Cmax\_pred based on the model prediction at 0 minutes.

**Table 14. R3G Plasma TK Parameters for Male Harlan Sprague Dawley Rats following a Single Gavage Administration of RES<sup>a,b</sup>**

Parameter	312.5 mg/kg	625 mg/kg	1250 mg/kg
Cmax_obs (ng/mL) <sup>c</sup>	38000	38200	80200
Cmax_pred (ng/mL)	30100 ± 5800	31700 ± 4700	64200 ± 9600
Tmax_obs (min) <sup>c</sup>	180	180	480
Tmax_pred (min)	145 ± 35	146 ± 27	338 ± 50
K10 (min <sup>-1</sup> )	0.00199 ± 0.00067	0.00183 ± 0.00050	0.000668 ± 0.000577
K10_Half-life (min)	348 ± 116	379 ± 104	1040 ± 890
AUC_0-T (ng/mL·min) <sup>c</sup>	19900000	23000000	52900000
AUCinf_pred (ng/mL·min)	20200000 ± 3800000	22700000 ± 3500000	120000000 ± 71000000

- Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- Observed values do not have a reported SEM.

**Table 15. R3G Plasma TK Parameters for Female Harlan Sprague Dawley Rats following a Single Gavage Administration of RES<sup>a,b</sup>**

Parameter	312.5 mg/kg	625 mg/kg	1250 mg/kg
Cmax_obs (ng/mL) <sup>c</sup>	39900	68300	89400
Cmax_pred (ng/mL)	28600 ± 5000	60100 ± 10200	67000 ± 11400
Tmax_obs (min) <sup>c</sup>	360	480	360
Tmax_pred (min)	124 ± 30	173 ± 34	248 ± 43
K10 (min <sup>-1</sup> )	0.000961 ± 0.000485	0.00262 ± 0.00081	0.000934 ± 0.000598
K10_Half-life (min)	721 ± 364	265 ± 82	742 ± 474
AUC_0-T (ng/mL·min) <sup>c</sup>	23000000	35600000	53000000
AUCinf_pred (ng/mL·min)	33500000 ± 11800000	36100000 ± 5700000	90400000 ± 35900000

- Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- Observed values do not have a reported SEM.

**Table 16. R3G Plasma TK Parameters for B6C3F1/N Mice following a Single IV Administration of RES to Males and Females (10 mg/kg)<sup>a,b</sup>**

<b>Parameter</b>	<b>Males</b>	<b>Females</b>
Cmax_obs (ng/mL) <sup>c</sup>	10400	12900
Cmax_pred (ng/mL) <sup>d</sup>	141000 ± 326000	27900 ± 40000
Alpha_Half-life (min)	1.19 ± 0.83	2.83 ± 2.52
Beta_Half-life (min)	105 ± 16	72.7 ± 10.3
K10 (min <sup>-1</sup> )	0.312 ± 0.443	0.0874 ± 0.103
K10_Half-life (min)	2.22 ± 3.14	7.93 ± 9.30
K12 (min <sup>-1</sup> )	0.263 ± 0.076	0.140 ± 0.129
K21 (min <sup>-1</sup> )	0.0123 ± 0.0090	0.0267 ± 0.0126
AUC_0-T (ng/mL·min) <sup>c</sup>	865000	1110000
AUCinf_pred (predicted) (ng/mL·min)	453000 ± 404000	320000 ± 96000
MRT (min)	71.6 ± 64.1	71.5 ± 20.8

- a. Based on a two-compartment model with bolus input, first order output, and 1/Yhat<sup>2</sup> weighting.
- b. Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- c. Observed values do not have a reported SEM.
- d. Cmax\_pred based on the model prediction at 0 minutes.

**Table 17. R3G Plasma TK Parameters for Male B6C3F1/N Mice following a Single Gavage Administration of RES<sup>a,b</sup>**

Parameter	625 mg/kg	1250 mg/kg	2500 mg/kg
Cmax_obs (ng/mL) <sup>c</sup>	26400	36700	61200
Cmax_pred (ng/mL)	24000 ± 4700	38100 ± 10700	56300 ± 14400
Tmax_obs (min) <sup>c</sup>	90.0	480	360
Tmax_pred (min)	28.3 ± 17.1	105 ± 37	160 ± 42
K10 (min <sup>-1</sup> )	0.00139 ± 0.00071	0.00230 ± 0.00130	0.00239 ± 0.00168
K10_Half-life (min)	499 ± 255	302 ± 170	290 ± 203
AUC_0-T (ng/mL·min) <sup>c</sup>	11100000	16500000	33200000
AUCinf_pred (ng/mL·min)	18000000 ± 7000000	21100000 ± 6200000	34500000 ± 9900000

- Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- Observed values do not have a reported SEM.

**Table 18. R3G Plasma TK Parameters for Female B6C3F1/N Mice following a Single Gavage Administration of RES<sup>a,b</sup>**

Parameter	625 mg/kg	1250 mg/kg	2500 mg/kg
Cmax_obs (ng/mL) <sup>c</sup>	39300	35500	104000
Cmax_pred (ng/mL)	32100 ± 7800	30000 ± 6500	76600 ± 18600
Tmax_obs (min) <sup>c</sup>	240	360	360
Tmax_pred (min)	49.7 ± 22.5	60.6 ± 23.3	180 ± 43
K10 (min <sup>-1</sup> )	0.00279 ± 0.00097	0.00147 ± 0.00082	0.00269 ± 0.00214
K10_Half-life (min)	248 ± 86	472 ± 263	258 ± 205
AUC_0-T (ng/mL·min) <sup>c</sup>	12900000	14500000	31200000
AUCinf_pred (ng/mL·min)	13200000 ± 3100000	22300000 ± 8800000	46200000 ± 12200000

- Based on a one-compartment model with first order input, first order output, and 1/Yhat<sup>2</sup> weighting.
- Parameter estimates are reported to three significant figures as estimate ± standard error of the mean (SEM).
- Observed values do not have a reported SEM.