Supplementary data: Table 1. Hematology

Sex	Males					Females				
Dose level (mg/kg/day)	**0**	**0.5**	**5**	**50**	**250**	**0**	**0.5**	**5**	**50**	**250**
No. of animals	**10**	**10**	**10**	**10**	**10**	**9**	**10**	**10**	**10**	**10**
RBC ($x10^6/\mu L$)	9.00 ± 0.51	8.89 ± 0.68	9.14 ± 0.57	9.09 ± 0.34	9.29 ± 0.62	9.06 ± 0.77	8.89 ± 0.37	8.89 ± 0.47	8.99 ± 0.49	8.87 ± 0.34
HGB (g/dL)	16.3 ± 0.8	15.9 ± 0.8	16.1 ± 0.4	16.5 ± 0.6	17.0 ± 0.5*	16.8 ± 0.9	16.4 ± 0.5	16.4 ± 0.8	16.5 ± 0.7	16.6 ± 0.8
HCT (%)	50.9 ± 3.2	49.0 ± 2.8	50.0 ± 1.6	51.2 ± 1.5	52.8 ± 2.1	51.2 ± 3.1	50.2 ± 1.6	49.8 ± 2.8	50.8 ± 2.2	50.5 ± 2.3
MCV (fL)	56.5 ± 1.6	55.2 ± 1.9	54.8 ± 2.1	56.4 ± 1.3	56.9 ± 1.7	56.6 ± 2.4	56.5 ± 2.1	56.0 ± 1.4	56.5 ± 2.0	56.9 ± 1.8
MCH (pg)	18.1 ± 0.4	17.8 ± 0.6	17.6 ± 0.8	18.1 ± 0.4	18.4 ± 0.9	18.6 ± 0.8	18.5 ± 0.6	18.5 ± 0.4	18.4 ± 0.6	18.8 ± 0.9
MCHC (g/dL)	32.0 ± 0.5	32.4 ± 0.3	32.1 ± 0.6	32.2 ± 0.5	32.3 ± 0.6	32.9 ± 0.4	32.7 ± 0.4	33.0 ± 0.8	32.5 ± 0.3	32.9 ± 0.9
PLT ($10^3/\mu L$)	986 ± 88.56	1054.1 ± 121.39	1051.1 ± 90.19	1054.7 ± 59.83	1016.2 ± 65.25	890.9 ± 171.59	922.8 ± 102.96	936.0 ± 127.65	1074.8 ± 205.20	922.8 ± 200.19
WBC ($x10^3/\mu L$)	10.16 ± 1.853	11.25 ± 2.124	12.22 ± 2.776	13.85 ± 3.271*	14.58 ± 2.971**	5.43 ± 1.866	7.99 ± 1.318	8.28 ± 2.113	9.82 ± 2.431**	12.29 ± 5.087**
NEU (%)	16.9 ± 4.44	15.5 ± 3.91	13.7 ± 4.01	12.7 ± 3.41*	8.8 ± 2.48**	12.4 ± 3.84	12.4 ± 5.81	10.8 ± 3.22	10.1 ± 3.52	7.3 ± 3.18*
LYM (%)	76.3 ± 4.99	78.2 ± 4.07	79.1 ± 4.94	81 ± 4.19	85.0 ± 2.62**	81.3 ± 4.73	81.8 ± 6.06	82.6 ± 4.92	83.3 ± 5.29	86.5 ± 3.13
MON (%)	3.6 ± 1.25	3.3 ± 0.78	4 ± 0.89	3.7 ± 1.30	3.4 ± 0.68	2.6 ± 0.46	3.0 ± 0.79	3.7 ± 1.83	3.4 ± 1.32	3.0 ± 0.59
EOS (%)	1.4 ± 0.38	1.2 ± 0.52	0.8 ± 0.21**	0.9 ± 0.29**	0.8 ± 0.30**	1.4 ± 0.51	1.0 ± 0.35	1.0 ± 0.39	1.0 ± 0.38	1.0 ± 0.24
BAS (%)	0.4 ± 0.11	0.4 ± 0.13	0.4 ± 0.07	0.4 ± 0.09	0.5 ± 0.09	0.7 ± 0.29	0.4 ± 0.21	0.5 ± 0.15	0.5 ± 0.10	0.5 ± 0.09
RET (%)	2.37 ± 0.312	2.53 ± 0.411	2.29 ± 0.268	2.51 ± 0.229	2.52 ± 0.275	2.67 ± 0.471	2.48 ± 0.260	2.52 ± 0.383	2.64 ± 0.460	2.96 ± 0.515
LUC% (%)	1.4 ± 0.44	1.4 ± 0.32	2.0 ± 0.68*	1.4 ± 0.45	1.6 ± 0.58	1.6 ± 1.05	1.3 ± 0.18	1.6 ± 0.47	1.8 ± 0.60	1.7 ± 0.48
NEU ($x10^3/\mu L$)	1.78 ± 0.805	1.74 ± 0.620	1.68 ± 0.671	1.74 ± 0.577	1.29 ± 0.483	0.65 ± 0.215	1.01 ± 0.565	0.88 ± 0.309	0.94 ± 0.226	0.82 ± 0.292
LYM ($x10^3/\mu L$)	7.67 ± 0.925	8.81 ± 1.810	9.67 ± 2.408	11.27 ± 2.946**	12.37 ± 2.430**	4.45 ± 1.709	6.52 ± 1.068	6.85 ± 1.822	8.26 ± 2.471**	10.71 ± 4.718**
MON ($x10^3/\mu L$)	0.37 ± 0.155	0.36 ± 0.077	0.49 ± 0.143	0.48 ± 0.123	0.49 ± 0.112	0.14 ± 0.042	0.24 ± 0.075	0.30 ± 0.152**	0.32 ± 0.115**	0.36 ± 0.150**
EOS ($x10^3/\mu L$)	0.14 ± 0.045	0.13 ± 0.051	0.1 ± 0.022	0.12 ± 0.044	0.12 ± 0.060	0.07 ± 0.022	0.08 ± 0.025	0.08 ± 0.044	0.10 ± 0.038	0.12 ± 0.059*
BAS ($x10^3/\mu L$)	0.04 ± 0.013	0.05 ± 0.020	0.05 ± 0.012	0.06 ± 0.012	0.08 ± 0.016+	0.04 ± 0.009	0.04 ± 0.013	0.04 ± 0.013	0.04 ± 0.013	0.06 ± 0.030
RET ($x10^9/\mu L$)	211.8 ± 21.91	224.1 ± 34.78	208.3 ± 17.49	227.8 ± 23.12	234.3 ± 29.10	240.1 ± 34.96	220.4 ± 21.94	224.4 ± 39.79	238.3 ± 46.18	262.8 ± 47.92
LUC ($x10^3/\mu L$)	0.14 ± 0.069	0.15 ± 0.032	0.25 ± 0.098*	0.19 ± 0.076	0.24 ± 0.114	0.08 ± 0.052	0.11 ± 0.023	0.13 ± 0.050	0.17 ± 0.045**	0.21 ± 0.113**
PT (sec)	14.9 ± 0.54	15.3 ± 0.61	15.3 ± 0.60	15.2 ± 0.64	14.9 ± 0.65	14.2 ± 0.33	14.4 ± 0.68	14.5 ± 0.60	14.3 ± 0.31	14.8 ± 0.53
APTT (sec)	18.5 ± 0.71	17.9 ± 0.69	17.5 ± 0.97	17.2 ± 0.92*	15.8 ± 1.41**	17.2 ± 1.32	16.0 ± 2.34	14.5 ± 1.44**	12.6 ± 1.23**	12.3 ± 2.04**

Each values represent the mean ± standard deviation (SD) $^{*}P < 0.05$, $^{**}P < 0.01$

Table 2. Clinical Chemistry

Sex	Males					Females				
Dose level (mg/kg/day)	**0**	**0.5**	**5**	**50**	**250**	**0**	**0.5**	**5**	**50**	**250**
No. of animals	**10**	**10**	**10**	**10**	**10**	**9**	**10**	**10**	**10**	**10**
GLU (mg/dL)	152.2 ± 24.92	148.1 ± 27.70	138 ± 32.96	124.6 ± 14.32	135.7 ± 20.88	99.4 ± 29.75	125.2 ± 35.38	108.1 ± 27.61	142.3 ± 31.84*	129.0 ± 36.69
BUN (mg/dL)	15.2 ± 1.65	15.7 ± 0.90	16.4 ± 0.97	14.3 ± 1.69	14 ± 1.21	16.3 ± 2.51	17.6 ± 1.57	19.3 ± 6.62	16.8 ± 2.79	17.2 ± 1.52
CREA (mg/dL)	0.57 ± 0.037	0.53 ± 0.030*	0.52 ± 0.026**	0.50 ± 0.037**	0.48 ± 0.021**	0.58 ± 0.047	0.61 ± 0.066	0.59 ± 0.087	0.57 ± 0.048	0.62 ± 0.073
TP (g/dL)	6.96 ± 0.189	6.71 ± 0.294	6.95 ± 0.431	7.17 ± 0.247	7.07 ± 0.233	7.54 ± 0.167	7.76 ± 0.314	7.57 ± 0.267	7.88 ± 0.333	7.61 ± 0.487
ALB (g/dL)	4.49 ± 0.123	4.36 ± 0.156	4.46 ± 0.264	4.5 ± 0.153	4.42 ± 0.089	4.93 ± 0.137	5.03 ± 0.266	4.84 ± 0.189	5.00 ± 0.254	4.77 ± 0.347
A/G (ratio)	1.82 ± 0.108	1.86 ± 0.089	1.79 ± 0.052	1.69 ± 0.065**	1.68 ± 0.104**	1.90 ± 0.119	1.85 ± 0.097	1.78 ± 0.098*	1.73 ± 0.125**	1.68 ± 0.081**
AST (IU/L)	131.9 ± 20.23	119.7 ± 14.45	129.7 ± 12.63	120.9 ± 6.23	114.2 ± 19.63*	140.8 ± 19.52	128.7 ± 20.45	129.8 ± 27.01	119.8 ± 23.70	105.2 ± 10.30+
ALT (IU/L)	31.8 ± 5.43	29.4 ± 4.20	28 ± 3.83	30.1 ± 3.02	31.6 ± 4.71	28.9 ± 8.04	34.4 ± 12.79	25.8 ± 4.69	22.4 ± 2.39	24.5 ± 2.44
TBIL (mg/dL)	0.138 ± 0.0245	0.171 ± 0.0284*	0.153 ± 0.0268	0.169 ± 0.0312*	0.174 ± 0.0257*	0.159 ± 0.0196	0.189 ± 0.0176	0.209 ± 0.0271**	0.226 ± 0.0305**	0.236 ± 0.0413**
GGT (IU/L)	0.69 ± 0.192	0.73 ± 0.250	0.7 ± 0.228	0.53 ± 0.190	1.11+D ± 0.187	1.19 ± 0.405	1.38 ± 0.556	1.23 ± 0.397	1.06 ± 0.366	2.23 ± 1.082
ALP (IU/L)	403.8 ± 70.89	400.4 ± 56.12	340.5 ± 78.05	359.8 ± 68.93	447.6 ± 61.65	257.6 ± 51.96	235.4 ± 88.44	238.8 ± 74.30	240.3 ± 75.71	351.9 ± 85.33*
TCHO (mg/dL)	78.9 ± 17.21	80.1 ± 23.20	83.3 ± 16.79	72.9 ± 8.24	75.4 ± 10.70	85.1 ± 23.62	88.1 ± 15.37	78.7 ± 18.08	80.5 ± 12.71	90.5 ± 18.63
TG (mg/dL)	29.3 ± 12.56	30.2 ± 12.56	56.3 ± 37.35	32 ± 19.04	34.4 ± 13.81	17.7 ± 8.55	22.0 ± 13.87	19.5 ± 6.42	24.7 ± 8.22	25.9 ± 7.36
Ca (mg/dL)	11.19 ± 0.535	11.38 ± 0.270	11.84 ± 0.561**	11.65 ± 0.461	11.86 ± 0.253**	11.21 ± 0.405	11.66 ± 0.503	11.70 ± 0.444	12.21 ± 0.271**	12.27 ± 0.602**
IP (mg/dL)	9.51 ± 0.777	9.51 ± 0.494	10.37 ± 0.633*	10.11 ± 0.761	10.40 ± 0.459*	7.95 ± 0.643	8.48 ± 0.733	8.78 ± 0.786	8.87 ± 0.874*	9.89 ± 0.626**
K (mmol/L)	7.37 ± 1.217	7.28 ± 0.989	6.86 ± 1.098	7.07 ± 0.700	7.25 ± 0.512	6.69 ± 1.242	6.68 ± 1.394	6.86 ± 0.860	6.50 ± 0.793	7.52 ± 0.880
CK (IU/L)	702.2 ± 157.65	556.9 ± 107.60	684.2 ± 156.32	603 ± 83.09	595.6 ± 112.75	841.2 ± 121.73	609.9 ± 181.42*	681.8 ± 251.80	675.3 ± 210.65	544.3 ± 108.90**
PL (mg/dL)	107.3 ± 18.04	108.1 ± 18.56	120.6 ± 25.07	106.4 ± 10.06	114 ± 11.94	149.0 ± 31.54	155.7 ± 24.54	140.6 ± 22.27	148.6 ± 17.42	159.6 ± 28.25
Na (mmol/L)	147 ± 1.05	146.5 ± 1.43	147.9 ± 1.66	147.9 ± 0.99	147.6 ± 0.97	146.9 ± 1.54	146.4 ± 1.17	146.2 ± 1.48	148.1 ± 1.37	146.8 ± 1.87
Cl (mmol/L)	102.4 ± 1.43	102.8 ± 1.14	102.2 ± 2.04	103.3 ± 1.57	102.5 ± 0.97	105.0 ± 1.41	103.9 ± 1.60	104.0 ± 1.76	103.6 ± 0.97	103.0 ± 1.41

Each values represent the mean ± standard deviation (SD). * $P < 0.05$, ** $P < 0.01$

Table 3. Sexual Maturation

Dose level (mg/kg/day)	0	0.5	5	50	250
Male					
Preputial separation days (age)	42.6 ± 1.51	41.78 ± 1.2	41.6 ± 1.58	42 ± 1.32	42.8 ± 1.23
Body weight on preputial Separation (g)	223.51 ± 10.2	219.46 ± 17.91	230.6 ± 10.88	226.81 ± 11.81	230.85 ± 11.53
No. of animals	10	9[a]	10	9[a]	10
Female					
Vaginal opening days (age)	32.2 ± 1.75	33 ± 2.16	33 ± 2.16	32.8 ± 1.48	30.4 ± 0.52**
Body weight on vaginal opening (g)	122.79 ± 9.26	126.2 ± 10.63	136.19 ± 16.99	125.04 ± 13.07	107.94 ± 5.89**
No. of animals	10	10	10	10	10

Each value represents the mean ± standard deviation (SD). Note. [a] One male was not conducted, * $P < 0.05$, ** $P < 0.01$

Table 4. Absolute Organ Weight

Sex	Males					Females				
Dose level (mg/kg/day)	**0**	**0.5**	**5**	**50**	**250**	**0**	**0.5**	**5**	**50**	**250**
No. of animals	**10**	**10**	**10**	**10**	**10**	**9**	**10**	**10**	**10**	**10**
Brain (g)	2.111 ± 0.0771	2.03 ± 0.1070	2.115 ± 0.1085	2.061 ± 0.0878	2.068 ± 0.0948	1.968 ± 0.0884	1.916 ± 0.0829	1.965 ± 0.1067	1.918 ± 0.1237	1.925 ± 0.0974
Heart (g)	1.535 ± 0.0746	1.581 ± 0.1362	1.665 ± 0.1691	1.593 ± 0.1179	1.551 ± 0.1149	0.97 ± 0.0821	0.998 ± 0.0963	0.996 ± 0.1329	0.966 ± 0.1061	1.017 ± 0.1082
Kidneys (g)	3.736 ± 0.4984	3.832 ± 0.4035	3.922 ± 0.2244	3.775 ± 0.3999	3.994 ± 0.3763	2.099 ± 0.2106	2.12 ± 0.2386	2.263 ± 0.2554	2.206 ± 0.2545	2.28 ± 0.2475
Liver (g)	15.551 ± 1.2632	16 ± 2.1637	16.635 ± 2.0775	14.634 ± 1.5160	14.632 ± 1.8167	8.725 ± 1.3748	8.389 ± 0.9823	8.708 ± 0.8852	8.306 ± 0.7173	9.233 ± 1.0952
Mammary gland (g)	3.884 ± 0.8036	3.541 ± 0.8268	4.477 ± 1.2666	2.915 ± 0.3961	2.374 ± 0.3649**	2.635 ± 0.8280	2.697 ± 0.5768	2.923 ± 0.8223	2.522 ± 1.2123	2.13 ± 0.4712
Lung (g)	1.683 ± 0.1054	1.752 ± 0.1795	1.821 ± 0.0780	1.822 ± 0.1506	1.868 ± 0.1194*	1.302 ± 0.1434	1.452 ± 0.1721	1.338 ± 0.0994	1.352 ± 0.1001	1.4 ± 0.0907
Thyroid and parathyroid glands (g)	0.021 ± 0.0061	0.018 ± 0.0051	0.019 ± 0.0048	0.018 ± 0.0053	0.022 ± 0.0037	0.018 ± 0.0029	0.017 ± 0.0036	0.017 ± 0.0041	0.016 ± 0.0037	0.017 ± 0.0035
Prostate (g)	0.553 ± 0.1028	0.593 ± 0.1680	0.544 ± 0.1614	0.51 ± 0.0847	0.518 ± 0.0776	-	-	-	-	-
L-Ovary (g)	-	-	-	-	-	0.049 ± 0.0178	0.044 ± 0.0118	0.048 ± 0.0093	0.039 ± 0.0104	0.052 ± 0.0098
R-Ovary (g)	-	-	-	-	-	0.048 ± 0.0080	0.044 ± 0.0103	0.051 ± 0.0076	0.045 ± 0.0094	0.052 ± 0.0103

Absolute organ weight in male and female rats. Each value represents the mean ± standard deviation (SD). *P < 0.05, +P < 0.01

Table 5. Relative Organ Weight

Sex	Males					Females				
Dose level (mg/kg/day)	0	0.5	5	50	250	0	0.5	5	50	250
No. of animals	10	10	10	10	10	9	10	10	10	10
Terminal body weight	502.9 ± 39.52	513.5 ± 32.21	535.4 ± 35.28	489.5 ± 25.88	482.6 ± 35.85	291.4 ± 30.69	287.8 ± 22.31	297.2 ± 27.05	280.7 ± 18.46	293.9 ± 22.73
Brain (g)	0.4216 ± 0.02994	0.3961 ± 0.02150	0.3959 ± 0.02093	0.4219 ± 0.02472	0.4302 ± 0.03170	0.6803 ± 0.05694	0.6693 ± 0.05672	0.6651 ± 0.05856	0.6858 ± 0.06103	0.6577 ± 0.04690
Heart (g)	0.3061 ± 0.01591	0.3079 ± 0.02017	0.3132 ± 0.04683	0.3255 ± 0.01714	0.3216 ± 0.01296	0.3341 ± 0.02368	0.3467 ± 0.02036	0.3352 ± 0.03078	0.344 ± 0.02874	0.3462 ± 0.02910
Kidneys (g)	0.7409 ± 0.05685	0.7462 ± 0.06289	0.7343 ± 0.04941	0.7711 ± 0.07078	0.8275 ± 0.04722**	0.7221 ± 0.04762	0.7359 ± 0.04437	0.7614 ± 0.04943	0.7851 ± 0.06244	0.776 ± 0.06096
Liver (g)	3.0941 ± 0.13416	3.1076 ± 0.27638	3.1046 ± 0.31496	2.9863 ± 0.22042	3.0245 ± 0.19442	2.9848 ± 0.23980	2.9106 ± 0.18904	2.9301 ± 0.13410	2.9585 ± 0.14680	3.1392 ± 0.23102
Mammary gland (g)	0.7732 ± 0.15578	0.687 ± 0.14318	0.8332 ± 0.21871	0.5975 ± 0.08977	0.4922 ± 0.06880**	0.9047 ± 0.29458	0.9373 ± 0.18312	0.9705 ± 0.20073	0.8886 ± 0.39156	0.7215 ± 0.13074
Lung (g)	0.3358 ± 0.02254	0.341 ± 0.02436	0.341 ± 0.01951	0.3732 ± 0.03863*	0.3884 ± 0.02948**	0.4475 ± 0.02705	0.5065 ± 0.06508	0.4519 ± 0.03654	0.4826 ± 0.03269	0.4774 ± 0.02434
Thyroid and parathyroid glands (g)	0.0041 ± 0.00111	0.0036 ± 0.00103	0.0036 ± 0.00075	0.0037 ± 0.00109	0.0047 ± 0.00080	0.0061 ± 0.00060	0.006 ± 0.00167	0.0056 ± 0.00136	0.0055 ± 0.00116	0.0058 ± 0.00111
Prostate (g)	0.1101 ± 0.01903	0.1162 ± 0.03446	0.1014 ± 0.02717	0.1041 ± 0.01457	0.1083 ± 0.02081	-	-	-	-	-
L-Ovary (g)	-	-	-	-	-	0.017 ± 0.00616	0.015 ± 0.00347	0.0164 ± 0.00375	0.0138 ± 0.00398	0.0177 ± 0.00348
R-Ovary (g)	-	-	-	-	-	0.0167 ± 0.00388	0.0151 ± 0.00285	0.017 ± 0.00232	0.0161 ± 0.00407	0.0177 ± 0.00286

Relative organ weight to terminal body weight in male and female rats. Each values represent the mean ± standard deviation (SD), *P < 0.05, +P < 0.01