Table 20 - 1 Blood biochemistry - Group mean values in female rats
After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined		ALP (U/L)	AST (U/L)	ALT (U/L)	GGTP (U/L)	Creat (mg/dL)	BUN (mg/dL)	TP (g/dL)	Alb (g/dL)	Glob (g/dL)	A/G ratio	Gluc (mg/dL)
0	10	Mean	203	62	20	0	0.30	20.4	6.03	4.10	1.93	2.12	125
		S.D.	35	11	2	0	0.05	4.2	0.33	0.25	0.11	0.10	13
8	10	Mean	220	63	20	0	0.31	20.5	5.84	3.95	1.89	2.10	121
		S.D.	40	8	4	0	0.05	3.0	0.36	0.20	0.18	0.14	20
40	10	Mean	238	63	18	1	0.33	20.8	5.87	3.98	1.89	2.11	115
		S.D.	46	9	3	1	0.04	2.5	0.32	0.21	0.13	0.09	16
100	9	Mean	258	66	26	0	0.31	19.8	5.53 *	3.77	1.75 *	2.15	115
		S.D.	98	10	11	1	0.03	3.0	0.40	0.31	0.12	0.12	9

S.D. : Standard deviation.
Significantly different from control : *, p <= 0.05; **, p <= 0.01.

Table 20 - 2 Blood biochemistry - Group mean values in female rats
After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined		T.Chol (mg/dL)	TG (mg/dL)	T.Bil (mg/dL)	Ca (mg/dL)	P (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
0	10	Mean	44	11	0.05	10.0	6.3	145.9	3.36	111.2
		S.D.	13	3	0.01	0.3	0.9	1.9	0.32	1.5
8	10	Mean	46	12	0.05	9.9	6.4	145.4	3.32	110.8
		S.D.	9	5	0.01	0.2	1.0	1.4	0.23	2.2
40	10	Mean	47	12	0.05	9.9	6.5	145.4	3.34	111.0
		S.D.	9	5	0.01	0.2	0.7	1.3	0.08	1.6
100	9	Mean	42	14	0.05	9.8	6.8	145.1	3.66 *	110.5
		S.D.	11	5	0.01	0.4	1.0	1.8	0.25	1.5

S.D. : Standard deviation.
Significantly different from control : *, p <= 0.05; **, p <= 0.01.

Table 21 - 1 Organ weight - Group mean values in male rats
Absolute weight at terminal kill after 4 weeks of treatment

Dose (mg/kg/day)		Body weight (g)	Brain (mg)	Pituitary (mg)	Thymus (mg)	Thyroids (mg)	Heart (mg)	Lung (mg)	Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)	Salivary gland (mg)	Testes (mg)	Epididy-mides (mg)	Prostate (mg)	SV/CG (mg)
0	Mean	283	1878	8.5	425	17.8	792	1156	7.59	1980	570	69.0	614	3334	841	386	1087
	S.D.	15	80	1.3	111	1.9	70	74	0.62	194	85	16.8	84	251	88	91	230
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
8	Mean	283	1920	8.6	435	17.7	809	1148	7.73	2003	618	70.4	642	3118	788	355	990
	S.D.	14	68	0.8	99	2.8	54	108	0.46	143	90	9.1	65	264	78	86	214
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
40	Mean	274	1892	8.3	397	17.1	835	1134	7.12	1915	559	70.3	594	2959	780	351	1064
	S.D.	17	90	0.9	65	1.8	95	82	0.81	135	76	14.8	67	610	73	31	126
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
200/100	Mean	250	1860	7.8	372	20.1	749	1064	6.61 *	1831	504	66.1	557	3059	762	303	979
	S.D.	27	68	0.9	117	6.0	99	56	0.66	168	69	10.7	60	174	58	102	250
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

SV/CG: Seminal vesicle/Coagulating gland.
S.D.: Standard deviation.
N: Number of animals examined.
Significantly different from control: *, p <= 0.05; **, p <= 0.01.

Table 21 - 2 Organ weight - Group mean values in male rats
Relative weight to body weight(%) at terminal kill after 4 weeks of treatment

Dose (mg/kg/day)		Brain	Pituitary	Thymus	Thyroids	Heart	Lung	Liver	Kidneys	Spleen	Adrenals	Salivary gland	Testes	Epididy-mides	Prostate	SV/CG
0	Mean	0.664	0.0030	0.150	0.0063	0.279	0.409	2.68	0.699	0.201	0.0242	0.216	1.18	0.297	0.136	0.383
	S.D.	0.020	0.0004	0.038	0.0006	0.015	0.018	0.12	0.043	0.022	0.0049	0.021	0.07	0.025	0.027	0.071
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
8	Mean	0.680	0.0030	0.153	0.0063	0.286	0.406	2.73	0.708	0.219	0.0249	0.227	1.10	0.278	0.125	0.350
	S.D.	0.032	0.0003	0.028	0.0010	0.016	0.031	0.07	0.031	0.029	0.0032	0.018	0.07	0.018	0.027	0.073
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
40	Mean	0.692	0.0030	0.145	0.0063	0.304 *	0.414	2.59	0.699	0.204	0.0256	0.217	1.08	0.285	0.128	0.389
	S.D.	0.045	0.0003	0.023	0.0007	0.021	0.033	0.20	0.034	0.023	0.0049	0.020	0.22	0.031	0.009	0.053
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
200/100	Mean	0.749 *	0.0031	0.148	0.0082	0.300	0.429	2.65	0.736	0.201	0.0270	0.224	1.24	0.306	0.119	0.387
	S.D.	0.064	0.0003	0.040	0.0029	0.029	0.045	0.08	0.061	0.017	0.0068	0.016	0.16	0.022	0.031	0.062
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

Relative weight= (organ weight/body weight x 1000) x 100
SV/CG: Seminal vesicle/Coagulating gland.
S.D.: Standard deviation.
N: Number of animals examined.
Significantly different from control: *, p <= 0.05; **, p <= 0.01.

Table 21 - 3 Organ weight - Group mean values in male rats
At terminal kill after 4 weeks of treatment
Immunized group

Dose (mg/kg/day)		Body weight (g)	Thymus		Spleen	
			Absolute (mg)	Relative (%)	Absolute (mg)	Relative (%)
0	Mean	314	420	0.133	631	0.199
	S.D.	21	112	0.032	110	0.023
	N	8	8	8	8	8
8	Mean	311	470	0.152	623	0.200
	S.D.	21	59	0.020	85	0.015
	N	8	8	8	8	8
40	Mean	302	478	0.159	611	0.202
	S.D.	26	50	0.012	115	0.028
	N	8	8	8	8	8
200/100	Mean	287	336	0.118	610	0.213
	S.D.	17	47	0.023	32	0.008
	N	3	3	3	3	3

Relative weight= (organ weight/body weight x 1000) x 100
S.D.: Standard deviation.
N: Number of animals examined.

Table 22 - 1 Organ weight - Group mean values in female rats
Absolute weight at terminal kill after 4 weeks of treatment

Dose (mg/kg/day)		Body weight (g)	Brain (mg)	Pituitary (mg)	Thymus (mg)	Thyroids (mg)	Heart (mg)	Lung (mg)	Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)	Salivary gland (mg)	Ovary (mg)	Uterus (mg)
0	Mean	173	1714	10.5	376	13.4	563	890	5.00	1317	419	79.8	404	89.3	551
	S.D.	10	43	1.9	69	5.2	45	81	0.50	97	62	9.1	54	13.2	327
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
8	Mean	176	1779 **	9.5	383	13.5	581	894	4.88	1275	388	77.8	435	79.8	488
	S.D.	11	40	2.1	60	5.3	68	58	0.46	77	92	11.0	59	13.2	189
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
40	Mean	175	1767 *	9.9	361	11.8	581	907	4.75	1294	445	70.1	405	87.1	589
	S.D.	6	46	1.4	59	3.7	39	63	0.25	94	48	8.5	50	14.9	251
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
100	Mean	179	1750	10.4	342	11.7	603	900	5.02	1309	413	77.6	427	92.1	475
	S.D.	6	53	1.3	31	2.6	40	55	0.22	53	54	9.7	22	16.8	99
	N	9	9	9	9	9	9	9	9	9	9	9	9	9	9

S.D.: Standard deviation.
N: Number of animals examined.
Significantly different from control: *, p <= 0.05; **, p <= 0.01.

Table 22 - 2 Organ weight - Group mean values in female rats
Relative weight to body weight(%) at terminal kill after 4 weeks of treatment

Dose (mg/kg/day)		Brain	Pituitary	Thymus	Thyroids	Heart	Lung	Liver	Kidneys	Spleen	Adrenals	Salivary gland	Ovary	Uterus
0	Mean	0.991	0.0061	0.216	0.0077	0.325	0.514	2.88	0.760	0.241	0.0461	0.233	0.0515	0.318
	S.D.	0.044	0.0011	0.035	0.0027	0.019	0.041	0.24	0.043	0.026	0.0050	0.028	0.0065	0.191
	N	10	10	10	10	10	10	10	10	10	10	10	10	10
8	Mean	1.015	0.0054	0.217	0.0076	0.331	0.510	2.77	0.728	0.222	0.0441	0.247	0.0452	0.277
	S.D.	0.071	0.0010	0.025	0.0028	0.032	0.040	0.12	0.060	0.054	0.0045	0.022	0.0060	0.103
	N	10	10	10	10	10	10	10	10	10	10	10	10	10
40	Mean	1.010	0.0056	0.206	0.0068	0.333	0.518	2.71	0.739	0.254	0.0400	0.232	0.0499	0.339
	S.D.	0.040	0.0007	0.031	0.0022	0.025	0.030	0.12	0.037	0.026	0.0048	0.028	0.0092	0.152
	N	10	10	10	10	10	10	10	10	10	10	10	10	10
100	Mean	0.981	0.0058	0.192	0.0066	0.338	0.504	2.82	0.734	0.231	0.0435	0.239	0.0515	0.266
	S.D.	0.031	0.0007	0.018	0.0014	0.025	0.029	0.12	0.033	0.028	0.0056	0.013	0.0086	0.054
	N	9	9	9	9	9	9	9	9	9	9	9	9	9

Relative weight= (organ weight/body weight x 1000) x 100
S.D.: Standard deviation.
N: Number of animals examined.

Table 23 Cellularity - Group mean values in male rats

Dose (mg/kg/day)	No. of animals examined		/mg ($\times 10^6$)[a] Thymus	/mg ($\times 10^6$)[a] Spleen	/rat ($\times 10^7$) Thymus	/rat ($\times 10^7$) Spleen
0	10	Mean	2.593	0.526	112.4	30.1
		S.D.	0.436	0.067	41.2	6.3
8	10	Mean	2.644	0.564	117.2	35.3
		S.D.	0.279	0.091	36.9	9.8
40	10	Mean	2.590	0.484	104.6	27.0
		S.D.	0.341	0.071	29.7	4.8
200/100	6	Mean	2.479	0.506	96.3	25.4
		S.D.	0.473	0.083	48.7	4.8

S.D.: Standard deviation.
a: Number of lymphocytes/mg organ weight.

Table 24 Cellularity - Group mean values in female rats

Dose (mg/kg/day)	No. of animals examined		/mg ($\times 10^6$)[a] Thymus	/mg ($\times 10^6$)[a] Spleen	/rat ($\times 10^7$) Thymus	/rat ($\times 10^7$) Spleen
0	10	Mean	2.971	0.578	112.6	24.4
		S.D.	0.481	0.084	33.4	6.1
8	10	Mean	2.804	0.596	107.8	24.0
		S.D.	0.379	0.134	24.3	8.1
40	10	Mean	2.674	0.660	97.4	29.1
		S.D.	0.466	0.126	28.6	4.5
100	9	Mean	2.594	0.633	88.6	26.0
		S.D.	0.471	0.114	17.6	5.3

S.D.: Standard deviation.
a: Number of lymphocytes/mg organ weight.

Table 25 - 1 Summary - Flow cytometric analysis of thymic lymphocytes in male rats

Dose (mg/kg/day)	Number of animals examined		Number of thymic lymphocyte($\times 10^7$/rat)			
			Immature cells		Mature cells	
			DN cell (CD4-8-)	DP cell (CD4+8+)	Helper-Tcell (CD4+8-)	Cytotoxic-Tcell (CD4-8+)
0	10	Mean	1.6	65.0	7.0	3.1
		S.D.	0.5	25.0	2.6	1.2
8	10	Mean	1.8	67.2	6.8	3.0
		S.D.	0.7	22.7	1.7	1.1
40	10	Mean	1.7	58.7	5.7	2.4
		S.D.	0.3	19.3	1.4	0.9
200/100	6	Mean	2.0	51.8	5.3	2.2
		S.D.	1.2	25.6	3.4	1.6

S.D.: Standard deviation.
Immature cells: DN; Double negative, DP; Double positive.

Table 25 - 2 Summary - Flow cytometric analysis of splenic lymphocytes in male rats

Dose (mg/kg/day)	Number of animals examined		Number of splenic lymphocyte($\times 10^7$/rat)				
			Pan-Tcell (CD3+)	Pan-Bcell (CD45RA+)	Helper-Tcell (CD4+8-)	Cytotoxic-Tcell (CD4-8+)	NK cell (NKR P1A+)
0	10	Mean	2.9	4.1	4.6	2.2	0.9
		S.D.	0.7	1.0	1.1	0.7	0.3
8	10	Mean	3.5	5.0	5.7	2.7	1.0
		S.D.	0.9	1.7	1.7	1.1	0.4
40	10	Mean	2.4	3.4	4.5	2.2	0.8
		S.D.	0.6	1.0	0.9	0.7	0.1
200/100	6	Mean	1.8 *	3.4	3.9	1.8	0.8
		S.D.	0.3	0.7	1.0	0.5	0.1

S.D.: Standard deviation.
Significantly different form control: *, p<=0.05; **, p<=0.01.

Table 26 - 1 Summary - Flow cytometric analysis of thymic lymphocytes in female rats

Dose (mg/kg/day)	Number of animals examined		Number of thymic lymphocyte($\times 10^7$/rat)			
			Immature cells		Mature cells	
			DN cell (CD4-8-)	DP cell (CD4+8+)	Helper-Tcell (CD4+8-)	Cytotoxic-Tcell (CD4-8+)
0	10	Mean	1.4	63.3	5.9	3.1
		S.D.	0.6	22.2	2.4	1.0
8	10	Mean	1.5	58.7	6.7	3.1
		S.D.	0.3	15.8	1.6	0.9
40	10	Mean	1.3	53.8	4.6	1.9 **
		S.D.	0.5	17.6	1.5	0.7
100	9	Mean	1.3	47.6	5.0	2.0 *
		S.D.	0.4	9.9	1.5	0.6

S.D.: Standard deviation.
Immature cells: DN; Double negative, DP; Double positive.
Significantly different form control: *, p<=0.05; **, p<=0.01.

Table 26 - 2 Summary - Flow cytometric analysis of splenic lymphocytes in female rats

Dose (mg/kg/day)	Number of animals examined		Number of splenic lymphocyte($\times 10^7$/rat)				
			Pan-Tcell (CD3+)	Pan-Bcell (CD45RA+)	Helper-Tcell (CD4+8-)	Cytotoxic-Tcell (CD4-8+)	NK cell (NKR P1A+)
0	10	Mean	1.6	3.1	4.4	1.6	0.6
		S.D.	0.5	0.9	1.4	0.6	0.2
8	10	Mean	1.8	3.1	4.3	1.6	0.6
		S.D.	0.6	1.1	1.4	0.6	0.2
40	10	Mean	2.6 **	4.1 *	5.3	2.0	0.7
		S.D.	0.7	0.6	1.2	0.7	0.2
100	9	Mean	1.9	4.2 *	4.2	1.6	0.7
		S.D.	0.6	0.9	0.9	0.5	0.2

S.D.: Standard deviation.
Significantly different form control: *, p<=0.05; **, p<=0.01.

Table 27 Anti-SRBC IgM antibody titers - Group mean values in male rats
Immunized group

Dose (mg/kg/day)		IgM antibody titer (Serum dilution)
0	Mean	1184.1
	S.D.	905.3
	N	8
8	Mean	13125.8
	S.D.	23211.3
	N	8
40	Mean	424.3
	S.D.	286.5
	N	8
200/100	Mean	623.9
	S.D.	271.7
	N	3

S.D.: Standard deviation.
N: Number of animals examined.

Table 28 - 1 Necropsy - Incidence of macroscopic lesions in male rats
Terminal kill after 4 weeks of treatment

Site & Lesion	Dose (mg/kg/day)	0	8	40	200/100 a	
	No. of animals examined	10	10	10	6	
Lung :	[N=]	10	10	10	6	
Spot(s)		1	0	1	1	
Stomach :	[N=]	10	10	10	6	
Distention		0	4	1	0	
Small intestine :	[N=]	10	10	10	6	
Luminal dilatation		0	0	1	6	**
Liver:	[N=]	10	10	10	6	
Hepatodiaphragmatic nodule		0	0	0	1	
Kidney :	[N=]	10	10	10	6	
Pelvic dilatation		1	1	1	0	
Testis:	[N=]	10	10	10	6	
Softening		0	0	1	0	
Epididymis :	[N=]	10	10	10	6	
Softening		0	0	1	0	

a:The dose was changed from 200 mg/kg/day to 100 mg/kg/day at week 1.
[N=]: Number of animals examined at the site.
Significantly different from control: *, p <=0.05; **, p <=0.01.

Table 28 - 2 Necropsy - Incidence of macroscopic lesions in male rats
Killed *in extremis* or found dead

Site & Lesion	Dose (mg/kg/day)	0	8	40	200/100 a
	No. of animals examined	0	0	0	4
Systemic/external appearance :	[N=]	0	0	0	4
Emaciation		0	0	0	1
Soiled fur in perioral region		0	0	0	3
Soiled fur in abdominal region		0	0	0	2
Soiled fur in perianal region		0	0	0	2
Lung :	[N=]	0	0	0	4
Spot(s)		0	0	0	2
Consolidation		0	0	0	1
Stomach :	[N=]	0	0	0	4
Distention		0	0	0	2
Liquid contents		0	0	0	1
Small intestine :	[N=]	0	0	0	4
Distention		0	0	0	1
Liquid contents		0	0	0	1
Large intestine:	[N=]	0	0	0	4
Distention		0	0	0	2
Liquid contents		0	0	0	1

a:The dose was changed from 200 mg/kg/day to 100 mg/kg/day at week 1.
[N=]: Number of animals examined at the site.

Table 28 - 3 Necropsy - Incidence of macroscopic lesions in male rats
Terminal kill after 4 weeks of treatment
Immunized group

Site & Lesion	Dose (mg/kg/day)	0	8	40	200/100 a
	No. of animals examined	8	8	8	3
Lung:	[N=]	8	8	8	3
Spot(s)		0	1	0	0
Stomach :	[N=]	8	8	8	3
Distention		0	0	0	3 **
Small intestine :	[N=]	8	8	8	3
Luminal dilatation		0	0	0	3 **

a: The dose was changed from 200 mg/kg/day to 100 mg/kg/day at day 3.
[N=]: Number of animals examined at the site.
Significantly different from control: *, p <=0.05; **, p <=0.01.

Table 28 - 4 Necropsy - Incidence of macroscopic lesions in male rats
Killed *in extremis* or found dead
Immunized group

Site & Lesion	Dose (mg/kg/day)	0	8	40	200/100 a
	No. of animals examined	0	0	0	5
Systemic/external appearance :	[N=]	0	0	0	5
Emaciation		-	-	-	1
Soiled fur in perioral region		-	-	-	2
Soiled fur in nasorostral region		-	-	-	2
Soiled fur in abdominal region		-	-	-	1
Soiled fur in perianal region		-	-	-	2
Lung:	[N=]	0	0	0	5
Spot(s)		-	-	-	1
Consolidation		-	-	-	1
Stomach :	[N=]	0	0	0	5
Liquid contents		-	-	-	4
Small intestine :	[N=]	0	0	0	5
Liquid contents		-	-	-	5
Large intestine :	[N=]	0	0	0	5
Liquid contents		-	-	-	5

a: The dose was changed from 200 mg/kg/day to 100 mg/kg/day at day 3.
[N=]: Number of animals examined at the site.

Table 29 - 1 Necropsy - Incidence of macroscopic lesions in female rats
Terminal kill after 4 weeks of treatment

Site & Lesion	Dose (mg/kg/day)	0	8	40	100
	No. of animals examined	10	10	10	9
Lung :	[N=]	10	10	10	9
Spot(s)		1	2	0	2
Stomach :	[N=]	10	10	10	9
Distention		2	0	0	2
Small intestine :	[N=]	10	10	10	9
Luminal dilatation		0	0	0	2
Liver:	[N=]	10	10	10	9
Hepatodiaphragmatic nodule		0	0	1	0
Kidney :	[N=]	10	10	10	9
Pelvic dilatation		0	0	0	3
Uterus:	[N=]	10	10	10	9
Cyst(s)		0	0	0	1

[N=]: Number of animals examined at the site.

Table 29 - 2 Necropsy - Incidence of macroscopic lesions in female rats
Killed *in extremis* or found dead

Site & Lesion	Dose (mg/kg/day)	0	8	40	100
	No. of animals examined	0	0	0	1
Stomach :	[N=]	0	0	0	1
Liquid contents		0	0	0	1
Small intestine :	[N=]	0	0	0	1
Liquid contents		0	0	0	1
Large intestine:	[N=]	0	0	0	1
Liquid contents		0	0	0	1

[N=]: Number of animals examined at the site.