

Table 24

## Cellularity - Group mean values in female rats

Dose (mg/kg/day)	No. of animals examined		/mg ( $\times 10^6$ ) <sup>a</sup>		/rat ( $\times 10^7$ )	
			Thymus	Spleen	Thymus	Spleen
0	10	Mean	2.516	0.398	100.6	17.2
		S.D.	0.276	0.057	18.8	2.9
1	10	Mean	2.075	0.403	73.5 *	17.1
		S.D.	0.522	0.039	25.3	3.3
8	9	Mean	2.173	0.416	74.7	17.9
		S.D.	0.257	0.082	16.6	4.9
40	5	Mean	1.523 *	0.267 **	36.0 **	9.5 **
		S.D.	0.937	0.070	33.8	6.1

S.D.: Standard deviation.

a: Number of lymphocytes/mg organ weight.

Significantly different from control : \*,  $p \leq 0.05$  ; \*\*,  $p \leq 0.01$ .

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	1.7	45.7	6.5	1.8	
		S.D.	0.5	13.6	1.7	0.6	
1	10	Mean	2.2	53.6	7.4	1.6	
		S.D.	0.6	13.5	2.0	0.3	
8	10	Mean	1.5	42.6	5.9	1.4	
		S.D.	0.5	17.9	1.7	0.5	
40	4	Mean	1.4	41.8	6.6	1.6	
		S.D.	0.2	5.3	1.4	0.4	

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	2.6	3.8	1.7	0.8
		S.D.	0.8	0.9	0.9	0.6	0.2
1	10	Mean	3.1	2.7	4.0	1.7	0.8
		S.D.	0.6	1.2	0.9	0.4	0.4
8	10	Mean	3.1	2.7	4.3	2.0	0.9
		S.D.	0.6	1.0	0.8	0.7	0.3
40	4	Mean	2.3	2.2	3.5	1.6	0.7
		S.D.	0.4	0.6	0.7	0.5	0.2

S.D.: Standard deviation.

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	1.5	54.6	6.4	2.7	
		S.D.	0.3	12.2	1.9	0.8	
1	10	Mean	1.2	35.2 **	5.4	2.0 *	
		S.D.	0.4	14.3	2.0	0.8	
8	9	Mean	1.3	38.5 *	5.1	1.6 **	
		S.D.	0.2	9.5	0.8	0.3	
40	5	Mean	0.6 **	15.3 **	3.2 *	1.1 **	
		S.D.	0.4	18.7	2.3	0.7	

S.D.: Standard deviation.

Immature cells: DN; Double negative, DP; Double positive.

Significantly different from 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	1.0	1.5	2.0	1.2	0.4
		S.D.	0.3	0.3	0.4	0.3	0.1
1	10	Mean	1.1	1.7	2.2	1.1	0.5
		S.D.	0.4	0.4	0.6	0.4	0.1
8	9	Mean	1.1	1.6	2.4	1.1	0.6
		S.D.	0.5	0.6	1.0	0.5	0.1
40.	5	Mean	0.4 *	0.6 **	0.8 *	0.4 **	0.5
		S.D.	0.3	0.4	0.6	0.4	0.5

S.D.: Standard deviation.

Significantly different from control: \*,  $p \leq 0.05$ ; \*\*,  $p \leq 0.01$ .

Table 27 - 1      Anti-SRBC IgM antibody titers - Group mean values in male rats  
Immunized group

Dose (mg/kg/day)		IgM antibody titer (Serum dilution)
0	Mean	1124.7
	S.D.	561.6
	N	8
1	Mean	2194.7
	S.D.	2641.4
	N	8
8	Mean	2673.7
	S.D.	1590.8
	N	8
40	Mean	2184.7
	S.D.	1226.3
	N	3

S.D.: Standard deviation.

N: Number of animals examined.

Table 27 - 2      Anti-SRBC IgM antibody titers - Group mean values in female rats  
Immunized group

Dose (mg/kg/day)		IgM antibody titer (Serum dilution)
0	Mean	1637.1
	S.D.	1023.2
	N	8
0.2	Mean	5122.1
	S.D.	4362.5
	N	8
1	Mean	2655.7
	S.D.	3200.6
	N	8
8	Mean	1586.0
	S.D.	1610.3
	N	8
24	Mean	832.8
	S.D.	637.6
	N	7

S.D.: Standard deviation.

N: Number of animals examined.

Table 28 Hepatic oxidative stress marker - Group mean values in male rats  
After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined		Lipid peroxide contents (nmol/g tissue)	8-OHdG (ng/mg DNA)
0	10	Mean	626	1.88
		S.D.	371	0.53 (6)
1	10	Mean	549	1.71
		S.D.	195	0.48 (6)
8	10	Mean	457	2.08
		S.D.	125	0.33 (6)
40	4	Mean	500	1.94
		S.D.	86	0.21 (4)

S.D. : Standard deviation.

( ): Available number of animals for the parameter.



Table 29 Hepatic oxidative stress marker - Group mean values in female rats  
After 4 weeks of treatment

Dose (mg/kg/day)	No. of animals examined		Lipid peroxide contents (nmol/g tissue)	8-OHdG (ng/mg DNA)
0	10	Mean	372	1.32
		S.D.	176	0.21 (6)
1	10	Mean	264	1.37
		S.D.	36	0.23 (6)
8	9	Mean	268	1.49
		S.D.	106	0.31 (6)
40	5	Mean	453	1.73
		S.D.	200	0.84 (5)

S.D. : Standard deviation.

( ): Available number of animals for the parameter.

Table 30 - 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)	Salivary										SV/CG (mg)				
		Brain (mg)	Pituitary (mg)	Thymus (mg)	Thyroids (mg)	Heart (mg)	Lung (mg)	Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)		gland (mg)	Testes (mg)	Epididy- mides (mg)	Prostate (mg)
0	Mean	1883	8.9	371	23.1	953	1246	8.52	2089	549	81.7	663	3088	928	367	1142
	S.D.	75	0.9	85	4.1	95	129	0.61	125	75	9.5	75	209	101	61	161
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1	Mean	1893	8.7	411	20.5	962	1213	8.71	2169	580	72.6	627	3178	937	404	1165
	S.D.	64	0.9	71	3.6	93	62	0.84	167	88	6.7	76	326	109	80	114
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
8	Mean	1909	9.4	361	20.6	906	1191	8.14	2029	544	71.6 *	675	3223	970	385	1094
	S.D.	81	1.1	76	2.9	84	73	0.87	118	67	9.2	67	246	103	59	183
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
40	Mean	1909	9.2	363	19.9	909	1186	7.34 *	1928	500	71.0	626	3270	937	365	1032
	S.D.	54	1.4	57	3.1	131	68	0.89	265	57	5.6	29	239	85	44	110
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

SV/CG: Seminal vesicle/Coagulating gland.

S.D.: Standard deviation.

N: Number of animals examined.

Significantly different from control: \*,  $p \leq 0.05$ ; \*\*,  $p \leq 0.01$ .

Table 30 - 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)	Salivary gland													SV/CG		
	Brain	Pituitary	Thymus	Thyroids	Heart	Lung	Liver	Kidneys	Spleen	Adrenals	Testes	Epididy- mides	Prostate			
0	Mean	0.617	0.0029	0.121	0.0076	0.312	0.408	2.79	0.684	0.179	0.0268	0.217	1.01	0.305	0.120	0.376
	S.D.	0.024	0.0003	0.021	0.0015	0.029	0.039	0.11	0.034	0.020	0.0035	0.022	0.09	0.043	0.021	0.065
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1	Mean	0.614	0.0029	0.133	0.0067	0.312	0.394	2.82	0.703	0.188	0.0235 *	0.204	1.03	0.304	0.131	0.379
	S.D.	0.021	0.0003	0.017	0.0011	0.026	0.027	0.14	0.049	0.024	0.0021	0.027	0.08	0.031	0.024	0.048
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
8	Mean	0.634	0.0031	0.119	0.0068	0.300 *	0.395	2.69	0.672	0.180	0.0237 *	0.224	1.07	0.322	0.127	0.365
	S.D.	0.047	0.0003	0.022	0.0007	0.023	0.027	0.16	0.024	0.018	0.0029	0.019	0.10	0.037	0.015	0.073
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
40	Mean	0.651	0.0031	0.125	0.0068	0.309	0.404	2.50	0.654	0.170	0.0242	0.213	1.12	0.319	0.125	0.353
	S.D.	0.032	0.0004	0.025	0.0007	0.031	0.021	0.20	0.056	0.014	0.0014	0.006	0.07	0.024	0.020	0.048
	N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

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.

(IET 06-0070)

Table 30 - 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	343	522	0.152	641	0.187
	S.D.	14	111	0.028	63	0.022
	N	8	8	8	8	8
1	Mean	349	493	0.141	663	0.190
	S.D.	12	74	0.020	73	0.019
	N	8	8	8	8	8
8	Mean	332	437	0.132	696	0.210
	S.D.	16	103	0.028	71	0.017
	N	8	8	8	8	8
40	Mean	290	280	0.093	605	0.212
	S.D.	41	146	0.042	89	0.045
	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.

NA: Not available for statistical analysis.

Table 31 - 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		Salivary												
	(g)	(g)	Brain (mg)	Pituitary (mg)	Thymus (mg)	Thyroids (mg)	Heart (mg)	Lung (mg)	Liver (g)	Kidneys (mg)	Spleen (mg)	Adrenals (mg)	gland (mg)	Ovary (mg)	Uterus (mg)
0	Mean	191	1770	12.2	400	17.2	649	1045	5.37	1471	435	86.8	500	103.8	429
	S.D.	9	69	1.7	62	0.9	32	98	0.58	80	55	7.9	26	18.0	44
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1	Mean	188	1741	12.1	351	16.6	665	1029	4.95	1416	422	83.4	452 *	98.6	486
	S.D.	10	56	1.4	70	1.7	73	130	0.35	103	62	6.4	34	10.8	133
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
8	Mean	180	1751	10.9	341	15.4	607 *	997	4.64 **	1401	427	78.4	442 *	91.2	563
	S.D.	7	49	1.8	51	1.9	22	48	0.13	133	33	6.0	47	15.4	225
	N	9	9	9	9	9	9	9	9	9	9	9	9	9	9
40	Mean	164 *	1749	10.9	188 **	18.7	598	968	4.48 **	1279 **	327	95.2	434 *	93.1	420
	S.D.	21	62	2.0	110	6.0	55	128	0.50	115	147	15.7	63	20.0	228
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5

S.D.: Standard deviation.

N: Number of animals examined.

Significantly different from control: \*,  $p \leq 0.05$ ; \*\*,  $p \leq 0.01$ .

Table 31 - 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)	Salivary													
	Brain	Pituitary	Thymus	Thyroids	Heart	Lung	Liver	Kidneys	Spleen	Adrenals	gland	Ovary	Uterus	
0	Mean	0.930	0.0064	0.210	0.0090	0.341	0.549	2.82	0.773	0.228	0.0455	0.262	0.0544	0.226
	S.D.	0.047	0.0009	0.028	0.0006	0.028	0.056	0.26	0.053	0.028	0.0036	0.017	0.0089	0.029
	N	10	10	10	10	10	10	10	10	10	10	10	10	10
1	Mean	0.931	0.0064	0.187	0.0088	0.356	0.551	2.64	0.756	0.226	0.0445	0.241	0.0527	0.261
	S.D.	0.065	0.0006	0.031	0.0010	0.048	0.086	0.19	0.062	0.039	0.0037	0.024	0.0067	0.079
	N	10	10	10	10	10	10	10	10	10	10	10	10	10
8	Mean	0.972	0.0061	0.189	0.0085	0.337	0.554	2.57 *	0.777	0.237	0.0435	0.246	0.0506	0.314
	S.D.	0.046	0.0009	0.027	0.0010	0.011	0.037	0.07	0.070	0.017	0.0032	0.028	0.0083	0.132
	N	9	9	9	9	9	9	9	9	9	9	9	9	9
40	Mean	1.082 *	0.0066	0.109 **	0.0113	0.368	0.592	2.74	0.785	0.193	0.0592	0.266	0.0572	0.253
	S.D.	0.138	0.0005	0.054	0.0025	0.032	0.038	0.12	0.053	0.064	0.0134	0.037	0.0122	0.127
	N	5	5	5	5	5	5	5	5	5	5	5	5	5

Relative weight= (organ weight/body weight x 1000) x 100

S.D.: Standard deviation.

N: Number of animals examined.

Significantly different from control: \*, p <= 0.05; \*\*, p <= 0.01.

(IET 06-0070)

Table 31 - 3 Organ weight - Group mean values in female rats  
At terminal kill after 4 weeks of treatment  
Immunized group

Dose (mg/kg/day)	Body weight			Thymus		Spleen	
	(g)	Absolute (mg)	Relative (%)	Absolute (mg)	Relative (%)	Absolute (mg)	Relative (%)
0	Mean	206	430	0.208	484	0.234	
	S.D.	13	77	0.033	63	0.025	
	N	8	8	8	8	8	8
0.2	Mean	207	370	0.178	480	0.232	
	S.D.	13	54	0.019	40	0.018	
	N	8	8	8	8	8	8
1	Mean	206	425	0.206	499	0.242	
	S.D.	9	74	0.034	53	0.026	
	N	8	8	8	8	8	8
8	Mean	205	444	0.216	468	0.229	
	S.D.	13	80	0.030	47	0.026	
	N	8	8	8	8	8	8
24	Mean	200	385	0.187	468	0.232	
	S.D.	28	147	0.054	91	0.026	
	N	7	7	7	7	7	7

Relative weight= (organ weight/body weight x 1000) x 100

S.D.: Standard deviation.

N: Number of animals examined.

Table 32 - 1 Necropsy - Incidence of macroscopic lesions in male rats  
Terminal kill after 4 weeks of treatment

Site & Lesion	Dose (mg/kg/day)	0	1	8	40
	No. of animals examined	10	10	10	4
Small intestine :	[N=]	10	10	10	4
Distended with liquid		0	0	0	1
Large intestine :	[N=]	10	10	10	4
Distended with liquid		0	0	0	1
Kidney :	[N=]	10	10	10	4
Pelvic dilatation		1	0	0	0
Thyroid :	[N=]	10	10	10	4
Enlargement		1	0	0	0

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



Table 32 - 2 Necropsy - Incidence of macroscopic lesions in male rats  
Killed *in extremis* or found dead

Site & Lesion	Dose (mg/kg/day)	0	1	8	40
	No. of animals examined	0	0	0	6
Systemic/external appearance :	[N=]	0	0	0	6
Emaciation		-	-	-	1
Soiled fur in nasorostral region		-	-	-	2
Soiled fur in external genital region		-	-	-	1
Soiled fur in perianal region		-	-	-	4
Spleen :	[N=]	0	0	0	6
Atrophy		-	-	-	4
Thymus :	[N=]	0	0	0	6
Atrophy		-	-	-	5
Stomach :	[N=]	0	0	0	6
Distended with gas		-	-	-	6
Small intestine :	[N=]	0	0	0	6
Distended with gas		-	-	-	6
Large intestine :	[N=]	0	0	0	6
Distended with gas		-	-	-	6
Seminal vesicle :	[N=]	0	0	0	6
Atrophy		-	-	-	3
Coagulating gland :	[N=]	0	0	0	6
Atrophy		-	-	-	3

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

Table 32 - 3 Necropsy - Incidence of macroscopic lesions in male rats  
All animals examined

Site & Lesion	Dose (mg/kg/day)	0	1	8	40
		No. of animals examined			
Systemic/external appearance :	[N=]	10	10	10	10
Emaciation		0	0	0	1
Soiled fur in nasorostral region		0	0	0	2
Soiled fur in external genital region		0	0	0	1
Soiled fur in perianal region		0	0	0	4 *
Spleen :	[N=]	10	10	10	10
Atrophy		0	0	0	4 *
Thymus :	[N=]	10	10	10	10
Atrophy		0	0	0	5 *
Stomach :	[N=]	10	10	10	10
Distended with gas		0	0	0	6 **
Small intestine :	[N=]	10	10	10	10
Distended with gas		0	0	0	6 **
Distended with liquid		0	0	0	1
Large intestine :	[N=]	10	10	10	10
Distended with gas		0	0	0	6 **
Distended with liquid		0	0	0	1
Kidney :	[N=]	10	10	10	10
Pelvic dilatation		1	0	0	0
Seminal vesicle :	[N=]	10	10	10	10
Atrophy		0	0	0	3
Coagulating gland :	[N=]	10	10	10	10
Atrophy		0	0	0	3
Thyroid :	[N=]	10	10	10	10
Enlargement		1	0	0	0

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

Significantly different from control: \*,  $p \leq 0.05$ ; \*\*,  $p \leq 0.01$ .

Table 33 - 1 Necropsy - Incidence of macroscopic lesions in female rats  
Terminal kill after 4 weeks of treatment

Site & Lesion	Dose (mg/kg/day)	0	1	8	40
	No. of animals examined	10	10	9	5
Systemic/external appearance :	[N=]	10	10	9	5
Emaciation		0	0	0	2
Soiled fur in perioral region		0	0	0	1
Soiled fur in perianal region		0	0	0	1
Spleen :	[N=]	10	10	9	5
Atrophy		0	0	0	3 *
Thymus :	[N=]	10	10	9	5
Atrophy		0	0	0	3 *
Lung :	[N=]	10	10	9	5
Spot(s)		0	1	3	0
Small intestine :	[N=]	10	10	9	5
Distended with gas		0	0	0	3 *
Large intestine :	[N=]	10	10	9	5
Distended with gas		0	0	0	1
Kidney :	[N=]	10	10	9	5
Mass(es)		0	0	1	0
Uterus :	[N=]	10	10	9	5
Amputation		0	0	1	0

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

Significantly different from control: \*,  $p \leq 0.05$ ; \*\*,  $p \leq 0.01$ .

Table 33 - 2 Necropsy - Incidence of macroscopic lesions in female rats  
Killed *in extremis* or found dead

Site & Lesion	Dose (mg/kg/day)	0	1	8	40
	No. of animals examined	0	0	1	5
Systemic/external appearance :	[N=]	0	0	1	5
Emaciation		-	-	1	3
Soiled fur in perioral region		-	-	0	1
Soiled fur in nasorostral region		-	-	0	1
Soiled fur in perianal region		-	-	0	4
Spleen :	[N=]	0	0	1	5
Atrophy		-	-	1	5
Thymus :	[N=]	0	0	1	5
Atrophy		-	-	1	4
Stomach :	[N=]	0	0	1	5
Distended with gas		-	-	0	4
Distended with liquid		-	-	0	1
Small intestine :	[N=]	0	0	1	5
Distended with gas		-	-	1	5
Large intestine :	[N=]	0	0	1	5
Distended with gas		-	-	1	5
Distended with liquid		-	-	0	1
Liver :	[N=]	0	0	1	5
Spot(s)		-	-	0	1
Adrenal :	[N=]	0	0	1	5
Enlargement		-	-	0	1

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