REGULATORY REFERENCES

1) OECD Principles of Good Laboratory Practice: Document # 1, ENV/MC/CHEM (98)17.

2) OECD Guideline for the Testing of Chemicals (No. 471, Section 4: Health Effects) "Bacterial Reverse Mutation Test" Adopted on 21st July 1997.

3) Revised methods for the Salmonella mutagenicity test, D.M.Maron and B.N.Ames, Mutation Research, 113 pg 207 (1983).

4) Recommendations of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines for Laboratory Animal Facility published in The Gazette of India, December 15, 1998.

TABLE NO.I

COLONY COUNTS OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Strain : TA 1535 **Experiment No.: 1**

Treatment	Group Number	Dose µg/plate	Number of Revertant Colonies						Induced Revertants
			S-9	Individual Colony Counts			Mean	± S.D.	
Test Item	I	5000	-	8	9	7	8.00	1.00	-3.00
			+	10	12	7	9.67	2.52	-2.33
	II	1666.66	-	11	12	12	11.67	0.58	0.67
			+	14	13	11	12.67	1.53	0.67
	III	555.55	-	12	13	11	12.00	1.00	1.00
			+	12	14	11	12.33	1.53	0.33
	IV	185.18	-	12	11	10	11.00	1.00	0.00
			+	13	10	12	11.67	1.53	-0.33
	V	61.72	-	13	11	14	12.67	1.53	1.67
			+	13	12	14	13.00	1.00	1.00
Distilled Water (Solvent Control)	VI	100 µl	-	11	10	12	11.00	1.00	0.00
			+	13	12	11	12.00	1.00	0.00
Sodium Azide	VII	0.5	-	400	416	404	406.67	8.33	395.67
2 Amino Anthracene		0.5	+	316	324	316	318.67	4.62	306.67
Untreated Control	VIII	-	-	9	8	9	8.67	0.58	-2.33
			+	10	11	9	10.00	1.00	-2.00

TABLE NO.I (Contd.)

COLONY COUNTS OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Strain : TA 97a **Experiment No.: 1**

Treatment	Group Number	Dose µg/plate	Number of Revertant Colonies						Induced Revertants
			S-9	Individual Colony Counts			Mean	± S.D.	
Test Item	I	5000	-	96	90	94	93.33	3.06	-11.67
			+	100	98	102	100.00	2.00	-6.33
	II	1666.66	-	101	103	102	102.00	1.00	-3.00
			+	109	102	104	105.00	3.61	-1.33
	III	555.55	-	100	108	104	104.00	4.00	-1.00
			+	108	106	106	106.67	1.15	0.33
	IV	185.18	-	107	109	102	106.00	3.61	1.00
			+	109	105	107	107.00	2.00	0.67
	V	61.72	-	105	108	106	106.33	1.53	1.33
			+	106	107	109	107.33	1.53	1.00
Distilled Water (Solvent Control)	VI	100 µl	-	102	104	109	105.00	3.61	0.00
			+	104	110	105	106.33	3.21	0.00
4 NQNO	VII	0.5	-	380	364	396	380.00	16.00	275.00
2 - AF (Positive Control)		10.0	+	1086	1044	1096	1075.33	27.59	969.00
Untreated Control	VIII	-	-	92	93	95	93.33	1.53	-11.67
			+	101	106	103	103.33	2.52	-3.00

TABLE NO.I (Contd.)

COLONY COUNTS OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Strain : TA 98 **Experiment No.: 1**

Treatment	Group Number	Dose µg/plate	Number of Revertant Colonies						Induced Revertants
			S-9	Individual Colony Counts			Mean	± S.D.	
Test Item	I	5000	-	26	27	26	26.33	0.58	-2.00
			+	27	28	29	28.00	1.00	-2.00
	II	1666.66	-	30	29	25	28.00	2.65	-0.33
			+	34	25	26	28.33	4.93	-1.67
	III	555.55	-	27	30	28	28.33	1.53	0.00
			+	33	29	28	30.00	2.65	0.00
	IV	185.18	-	29	29	30	29.33	0.58	1.00
			+	30	32	31	31.00	1.00	1.00
	V	61.72	-	28	28	30	28.67	1.15	0.33
			+	30	31	31	30.67	0.58	0.67
Distilled Water (Solvent Control)	VI	100 µl	-	29	28	28	28.33	0.58	0.00
			+	29	30	31	30.00	1.00	0.00
4 NQNO	VII	0.5	-	312	324	336	324.00	12.00	295.67
2 - AF (Positive Control)		10.0	+	1020	1088	1096	1068.00	41.76	1038.00
Untreated Control	VIII	-	-	25	27	27	26.33	1.15	-2.00
			+	28	29	27	28.00	1.00	-2.00

TABLE NO.I (Contd.)

COLONY COUNTS OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Strain : TA 100 **Experiment No.: 1**

Treatment	Group Number	Dose µg/plate	Number of Revertant Colonies						Induced Revertants
			S-9	Individual Colony Counts			Mean	± S.D.	
Test Item	I	5000	-	108	103	105	105.33	2.52	-1.33
			+	109	103	109	107.00	3.46	-2.00
	II	1666.66	-	108	106	105	106.33	1.53	-0.33
			+	110	106	109	108.33	2.08	-0.67
	III	555.55	-	112	107	114	111.00	3.61	4.33
			+	110	112	115	112.33	2.52	3.33
	IV	185.18	-	104	111	110	108.33	3.79	1.67
			+	112	108	107	109.00	2.65	0.00
	V	61.72	-	104	106	112	107.33	4.16	0.67
			+	112	114	109	111.67	2.52	2.67
Distilled Water (Solvent Control)	VI	100 µl	-	105	108	107	106.67	1.53	0.00
			+	109	110	108	109.00	1.00	0.00
MMS (µl/plate)	VII	1 µl	-	404	428	436	422.67	16.65	316.00
2 - AF (Positive Control)		10.0	+	1116	1096	1100	1104.00	10.58	995.00
Untreated Control	VIII	-	-	100	102	102	101.33	1.15	-5.33
			+	103	104	106	104.33	1.53	-4.67

TABLE NO.I (Contd.)

COLONY COUNTS OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Strain : TA 102 **Experiment No.: 1**

Treatment	Group Number	Dose µg/plate	Number of Revertant Colonies						Induced Revertants
			S-9	Individual Colony Counts			Mean	± S.D.	
Test Item	I	5000	-	268	298	288	284.67	15.28	-6.67
			+	260	278	288	275.33	14.19	-30.67
	II	1666.66	-	312	288	294	298.00	12.49	6.67
			+	340	316	292	316.00	24.00	10.00
	III	555.55	-	280	300	296	292.00	10.58	0.67
			+	320	300	280	300.00	20.00	-6.00
	IV	185.18	-	360	336	324	340.00	18.33	48.67
			+	324	300	296	306.67	15.14	0.67
	V	61.72	-	260	240	212	237.33	24.11	-54.00
			+	300	260	252	270.67	25.72	-35.33
Distilled Water (Solvent Control)	VI	100 µl	-	308	278	288	291.33	15.28	0.00
			+	316	298	304	306.00	9.17	0.00
MMS (µl/plate)	VII	1.0 µl	-	2628	2596	2776	2666.67	96.03	2375.33
DANTHRON (Positive Control)		30.0	+	1024	1044	1036	1034.67	10.07	728.67
Untreated Control	VIII	-	-	216	208	214	212.67	4.16	-78.67
			+	208	228	216	217.33	10.07	-88.67

TABLE NO.II

COLONY COUNTS OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Strain : TA 1535 **Experiment No.: 2**

Treatment	Group Number	Dose µg/plate	Number of Revertant Colonies						Induced Revertants
			S-9	Individual Colony Counts			Mean	± S.D.	
Test Item	I	5000	-	9	8	8	8.33	0.58	-3.00
			+	11	11	9	10.33	1.15	-2.00
	II	1666.66	-	12	11	12	11.67	0.58	0.33
			+	13	13	12	12.67	0.58	0.33
	III	555.55	-	11	12	13	12.00	1.00	0.67
			+	12	12	14	12.67	1.15	0.33
	IV	185.18	-	11	12	11	11.33	0.58	0.00
			+	12	13	11	12.00	1.00	-0.33
	V	61.72	-	13	12	14	13.00	1.00	1.67
			+	11	13	14	12.67	1.53	0.33
Distilled Water (Solvent Control)	VI	100 µl	-	12	10	12	11.33	1.15	0.00
			+	12	13	12	12.33	0.58	0.00
Sodium Azide	VII	0.5	-	404	412	406	407.33	4.16	396.00
2 Amino Anthracene		0.5	+	304	332	320	318.67	14.05	306.33
Untreated Control	VIII	-	-	8	10	9	9.00	1.00	-2.33
			+	9	11	10	10.00	1.00	-2.33

TABLE NO.II (Contd.)

COLONY COUNTS OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Strain : TA 97a **Experiment No.: 2**

Treatment	Group Number	Dose µg/plate	Number of Revertant Colonies						Induced Revertants
			S-9	Individual Colony Counts			Mean	± S.D.	
Test Item	I	5000	-	92	94	98	94.67	3.06	-10.00
			+	100	98	102	100.00	2.00	-6.33
	II	1666.66	-	103	101	103	102.33	1.15	-2.33
			+	107	105	103	105.00	2.00	-1.33
	III	555.55	-	101	107	105	104.33	3.06	-0.33
			+	108	104	107	106.33	2.08	0.00
	IV	185.18	-	106	108	104	106.00	2.00	1.33
			+	110	108	106	108.00	2.00	1.67
	V	61.72	-	106	108	106	106.67	1.15	2.00
			+	110	108	107	108.33	1.53	2.00
Distilled Water (Solvent Control)	VI	100 µl	-	103	105	106	104.67	1.53	0.00
			+	105	108	106	106.33	1.53	0.00
4 NQNO	VII	0.5	-	376	368	394	379.33	13.32	274.67
2 - AF (Positive Control)		10.0	+	1082	1052	1094	1076.00	21.63	969.67
Untreated Control	VIII	-	-	94	95	95	94.67	0.58	-10.00
			+	103	104	102	103.00	1.00	-3.33

TABLE NO.II (Contd.)

COLONY COUNTS OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Strain : TA 98 **Experiment No.: 2**

Treatment	Group Number	Dose µg/plate	Number of Revertant Colonies						Induced Revertants
			S-9	Individual Colony Counts			Mean	± S.D.	
Test Item	I	5000	-	25	26	27	26.00	1.00	-0.67
			+	28	26	28	27.33	1.15	-1.67
	II	1666.66	-	29	30	26	28.33	2.08	1.67
			+	32	25	27	28.00	3.61	-1.00
	III	555.55	-	29	30	28	29.00	1.00	2.33
			+	32	30	29	30.33	1.53	1.33
	IV	185.18	-	30	31	29	30.00	1.00	3.33
			+	30	33	31	31.33	1.53	2.33
	V	61.72	-	29	28	30	29.00	1.00	2.33
			+	32	30	31	31.00	1.00	2.00
Distilled Water (Solvent Control)	VI	100 µl	-	26	27	27	26.67	0.58	0.00
			+	30	29	28	29.00	1.00	0.00
4 NQNO 2 - AF (Positive Control)	VII	0.5 10.0	-	318	328	342	329.33	12.06	302.67
			+	1014	1096	1082	1064.00	43.86	1035.00
Untreated Control	VIII	-	-	26	27	25	26.00	1.00	-0.67
			+	27	27	28	27.33	0.58	-1.67

TABLE NO.II (Contd.)

COLONY COUNTS OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Strain : TA 100 **Experiment No.: 2**

Treatment	Group Number	Dose µg/plate	Number of Revertant Colonies						Induced Revertants
			S-9	Individual Colony Counts			Mean	± S.D.	
Test Item	I	5000	-	107	102	104	104.33	2.52	-2.67
			+	110	103	108	107.00	3.61	-2.00
	II	1666.66	-	108	107	105	106.67	1.53	-0.33
			+	110	105	108	107.67	2.52	-1.33
	III	555.55	-	110	108	114	110.67	3.06	3.67
			+	109	113	116	112.67	3.51	3.67
	IV	185.18	-	105	108	114	109.00	4.58	2.00
			+	112	110	110	110.67	1.15	1.67
	V	61.72	-	112	108	106	108.67	3.06	1.67
			+	110	110	114	111.33	2.31	2.33
Distilled Water (Solvent Control)	VI	100 µl	-	104	109	108	107.00	2.65	0.00
			+	110	107	110	109.00	1.73	0.00
MMS (µl/plate)	VII	1.0 µl	-	438	410	426	424.67	14.05	317.67
2 - AF (Positive Control)		10.0	+	1120	1094	1104	1106.00	13.11	997.00
Untreated Control	VIII	-	-	102	103	105	103.33	1.53	-3.67
			+	100	103	104	102.33	2.08	-6.67

TABLE NO.II (Contd.)

COLONY COUNTS OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Strain : TA 102 **Experiment No.: 2**

Treatment	Group Number	Dose µg/plate	Number of Revertant Colonies						Induced Revertants
			S-9	Individual Colony Counts			Mean	± S.D.	
Test Item	I	5000	-	266	296	290	284.00	15.87	-1.33
			+	264	288	282	278.00	12.49	-23.33
	II	1666.66	-	310	290	296	298.67	10.26	13.33
			+	314	302	334	316.67	16.17	15.33
	III	555.55	-	288	302	300	296.67	7.57	11.33
			+	324	300	292	305.33	16.65	4.00
	IV	185.18	-	340	324	320	328.00	10.58	42.67
			+	302	300	308	303.33	4.16	2.00
	V	61.72	-	282	240	262	261.33	21.01	-24.00
			+	298	260	270	276.00	19.70	-25.33
Distilled Water (Solvent Control)	VI	100 µl	-	300	274	282	285.33	13.32	0.00
			+	312	294	298	301.33	9.45	0.00
MMS (µl/plate)	VII	1.0 µl	-	2634	2752	2582	2656.00	87.11	2370.67
DANTHRON (Positive Control)		30.0	+	1052	1022	1036	1036.67	15.01	735.33
Untreated Control	VIII	-	-	220	222	228	223.33	4.16	-62.00
			+	214	226	223	221.00	6.24	-80.33

TABLE NO.III

SUMMARY DATA OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Experiment No.: 1

Treatment	Dose µg/plate	S-9	Mean Number of Revertants and S.D.									
			TA1535		TA97a		TA98		TA100		TA102	
			Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Test Item	5000	-	8.00	1.00	93.33	3.06	26.33	0.58	105.33	2.52	284.67	15.28
		+	9.67	2.52	100.00	2.00	28.00	1.00	107.00	3.46	275.33	14.19
	1666.66	-	11.67	0.58	102.00	1.00	28.00	2.65	106.33	1.53	298.00	12.49
		+	12.67	1.53	105.00	3.61	28.33	4.93	108.33	2.08	316.00	24.00
	555.55	-	12.00	1.00	104.00	4.00	28.33	1.53	111.00	3.61	292.00	10.58
		+	12.33	1.53	106.67	1.15	30.00	2.65	112.33	2.52	300.00	20.00
	185.18	-	11.00	1.00	106.00	3.61	29.33	0.58	108.33	3.79	340.00	18.33
		+	11.67	1.53	107.00	2.00	31.00	1.00	109.00	2.65	306.67	15.14
	61.72	-	12.67	1.53	106.33	1.53	28.67	1.15	107.33	4.16	237.33	24.11
		+	13.00	1.00	107.33	1.53	30.67	0.58	111.67	2.52	270.67	25.72
Distilled Water (Solvent Control)	100 µl	-	11.00	1.00	105.00	3.61	28.33	0.58	106.67	1.53	291.33	15.28
		+	12.00	1.00	106.33	3.21	30.00	1.00	109.00	1.00	306.00	9.17
MMS (µl/plate)	1.0	-	-	-	-	-	-	-	422.67	16.65	2666.67	96.03
4 NQNO	0.5	-			380.00	16.00	324.00	12.00	-	-	-	-
Sodium azide	0.5	-	406.67	8.33	-	-	-	-	-	-	-	-
2 - AF	10.0	+	-	-	1075.33	27.59	1068.00	41.76	1104.00	10.58	-	-
DANTHRON	30.0	+	-	-	-	-	-	-	-	-	1034.67	10.07
2 - AA	0.5	+	318.67	4.62	-	-	-	-	-	-	-	-
Positive Control			-	-	-	-	-	-	-	-	-	-
Untreated Control	-	-	8.67	0.58	93.33	1.53	26.33	1.15	101.33	1.15	212.67	4.16
		+	10.00	1.00	103.33	2.52	28.00	1.00	104.33	1.53	217.33	10.07

TABLE NO.IV

SUMMARY DATA OF HISTIDINE REVERTANTS IN *SALMONELLA*

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Experiment No.: 2

Treatment	Dose µg/plate	S-9	Mean Number of Revertants and S.D.									
			TA1535		TA97a		TA98		TA100		TA102	
			Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Test Item	5000	-	8.33	0.58	94.67	3.06	26.00	1.00	104.33	2.52	284.00	15.87
		+	10.33	1.15	100.00	2.00	27.33	1.15	107.00	3.61	278.00	12.49
	1666.66	-	11.67	0.58	102.33	1.15	28.33	2.08	106.67	1.53	298.67	10.26
		+	12.67	0.58	105.00	2.00	28.00	3.61	107.67	2.52	316.67	16.17
	555.55	-	12.00	1.00	104.33	3.06	29.00	1.00	110.67	3.06	296.67	7.57
		+	12.67	1.15	106.33	2.08	30.33	1.53	112.67	3.51	305.33	16.65
	185.18	-	11.33	0.58	106.00	2.00	30.00	1.00	109.00	4.58	328.00	10.58
		+	12.00	1.00	108.00	2.00	31.33	1.53	110.67	1.15	303.33	4.16
	61.72	-	13.00	1.00	106.67	1.15	29.00	1.00	108.67	3.06	261.33	21.01
		+	12.67	1.53	108.33	1.53	31.00	1.00	111.33	2.31	276.00	19.70
Distilled Water (Solvent Control)	100 µl	-	11.33	1.15	104.67	1.53	26.67	0.58	107.00	2.65	285.33	13.32
		+	12.33	0.58	106.33	1.53	29.00	1.00	109.00	1.73	301.33	9.45
MMS (µl/plate)	1.0	-	-	-	-	-	-	-	424.67	14.05	2656.00	87.11
4 NQNO	0.5	-			379.33	13.32	329.33	12.06	-	-	-	-
Sodium azide	0.5	-	407.33	4.16	-	-	-	-	-	-	-	-
2 - AF	10.0	+	-	-	1076.00	21.63	1064.00	43.86	1106.00	13.11	-	-
DANTHRON	30.0	+	-	-	-	-	-	-	-	-	1036.67	15.01
2 - AA	0.5	+	318.67	14.05	-	-	-	-	-	-	-	-
Positive Control			-	-	-	-	-	-	-	-	-	-
Untreated Control	-	-	9.00	1.00	94.67	0.58	26.00	1.00	103.33	1.53	223.33	4.16
		+	10.00	1.00	103.00	1.00	27.33	0.58	102.33	2.08	221.00	6.24

APPENDIX NO.I

DOSE RANGE FINDING STUDY

Laboratory Test Item Code : TAS/002/015
Test System : *Salmonella typhimurium*

Strain : TA 100

Treatment	Group Number	Dose µg/plate	Number of Revertant Colonies						Induced Revertants
			S-9	Individual Colony Counts			Mean	± S.D.	
Test Item	I	5000	-	98	98	94	96.67	2.31	-12.33
			+	112	106	104	107.33	4.16	-2.00
	II	1000	-	106	102	104	104.00	2.00	-5.00
			+	110	107	108	108.33	1.53	-1.00
	III	500	-	106	112	109	109.00	3.00	0.00
			+	106	110	112	109.33	3.06	0.00
	IV	100	-	107	111	108	108.67	2.08	-0.33
			+	107	114	108	109.67	3.79	0.33
	V	50	-	108	110	109	109.00	1.00	0.00
			+	114	112	112	112.67	1.15	3.33
	VI	10	-	112	114	108	111.33	3.06	2.33
			+	116	109	113	112.67	3.51	3.33
	VII	5	-	109	110	106	108.33	2.08	-0.67
			+	106	112	109	109.00	3.00	-0.33
	VIII	1	-	108	104	102	104.67	3.06	-4.33
			+	105	108	107	106.67	1.53	-2.67
Distilled Water (Solvent Control)	IX	100 µl	-	110	111	106	109.00	2.65	0.00
			+	112	106	110	109.33	3.06	0.00
Untreated Control	X	Untreated Control	-	104	107	109	106.67	2.52	-2.33
			+	110	108	108	108.67	1.15	-0.67

APPENDIX NO.II

HISTORICAL DATA OF NUMBER OF HISTIDINE REVERTANT COLONIES

Test System : *Salmonella typhimurium*

Strain : TA1535

Study Number	S-9	Untreated Control		Positive Control		Solvent Control (Negative Control)				Historical Data Made On
						Distilled Water		DMSO		
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	
Average	-	9.21	0.77	529.29	15.67	10.30	1.17	10.04	0.82	31-10-2013
17541	-	10.33	1.15	464.00	42.14	-	-	12.00	1.00	02-12-2013
	-	10.00	1.00	389.33	12.22	-	-	11.33	0.58	
17510	-	12.33	1.15	463.33	40.27	-	-	12.00	1.00	09-12-2013
	-	13.00	1.00	465.00	36.59	-	-	12.67	1.53	
17569	-	13.00	1.73	460.67	36.68	-	-	13.33	1.15	19-12-2013
	-	13.00	1.00	470.00	56.43	-	-	12.00	1.00	
17575	-	10.00	1.00	423.33	15.95	-	-	10.00	1.00	02-01-2014
	-	10.67	0.58	417.67	12.42	-	-	10.67	0.58	
17576	-	8.33	0.58	417.33	16.65	10.00	1.73	-	-	16-01-2014
	-	10.00	1.00	402.67	8.33	9.00	0.00	-	-	
17548	-	11.00	1.00	411.33	15.53	10.00	1.00	-	-	03-02-2014
	-	9.00	1.00	414.67	13.32	9.33	0.58	-	-	
17534	-	7.67	0.58	488.00	10.00	9.33	0.58	-	-	20-02-2014
	-	8.33	0.58	462.00	23.07	9.67	0.58	-	-	
17852	-	9.33	0.58	430.67	14.05	-	-	10.67	0.58	27-03-2014
	-	9.67	0.58	423.33	10.07	-	-	10.67	1.15	
17774	-	8.67	0.58	412.00	10.58	11.33	1.15	-	-	16-04-2014
	-	11.33	0.58	422.67	12.86	11.67	0.58	-	-	
17957	-	9.67	0.58	409.33	6.11	-	-	10.00	1.00	21-05-2014
	-	9.00	1.00	391.33	8.08	-	-	9.33	0.58	
17958	-	9.00	0.00	389.33	16.65	-	-	10.00	1.00	06-06-2014
	-	8.67	0.58	400.00	12.00	-	-	10.33	0.58	
Average	-	10.05	0.81	432.93	19.38	10.07	0.82	11.00	0.90	

Study Number	S-9	Solvent Control (Negative Control)		Historical Data Made On
		DMF		
		Mean	± SD	
Average	-	11.33	1.06	01-11-2012

APPENDIX NO.II (Contd.)

HISTORICAL DATA OF NUMBER OF HISTIDINE REVERTANT COLONIES

Test System : *Salmonella typhimurium*

Strain : TA1535

Study Number	S-9	Untreated Control		Positive Control		Solvent Control (Negative Control)				Historical Data Made On
						Distilled Water		DMSO		
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	
Average	+	10.07	0.93	344.47	17.38	11.13	1.23	10.97	1.18	31-10-2013
17541	+	11.00	1.00	318.67	15.14	-	-	13.00	1.00	02-12-2013
	+	10.67	1.15	330.67	14.05	-	-	12.33	0.58	
17510	+	12.00	1.00	311.33	3.06	-	-	13.00	1.00	09-12-2013
	+	13.33	2.08	312.00	9.17	-	-	13.00	1.00	
17569	+	12.00	1.00	313.33	3.06	-	-	13.33	0.58	19-12-2013
	+	12.67	1.15	312.67	6.11	-	-	13.33	2.08	
17575	+	10.33	0.58	321.67	18.50	-	-	10.33	0.58	02-01-2014
	+	11.00	0.00	318.00	20.88	-	-	10.67	1.15	
17576	+	9.33	0.58	321.33	24.44	10.33	0.58	-	-	16-01-2014
	+	9.67	0.58	302.67	6.11	9.33	0.58	-	-	
17548	+	11.33	1.15	302.00	13.11	12.00	1.00	-	-	03-02-2014
	+	9.67	1.15	317.33	6.11	11.00	1.00	-	-	
17534	+	8.67	0.58	325.33	10.07	10.00	1.00	-	-	20-02-2014
	+	8.67	0.58	314.67	8.33	10.33	1.15	-	-	
17852	+	10.33	0.58	320.00	4.00	-	-	10.67	0.58	27-03-2014
	+	10.67	0.58	321.33	8.33	-	-	11.00	1.00	
17774	+	10.67	0.58	312.00	10.58	11.00	1.00	-	-	16-04-2014
	+	12.33	0.58	322.00	12.49	12.33	2.08	-	-	
17957	+	10.67	0.58	312.00	8.00	-	-	11.00	2.00	21-05-2014
	+	9.67	1.53	313.33	12.22	-	-	10.33	0.58	
17958	+	9.33	0.58	313.33	10.07	-	-	10.67	0.58	06-06-2014
	+	9.00	1.00	313.33	8.33	-	-	11.00	0.00	
Average	+	10.57	0.85	317.11	10.85	10.83	1.07	11.64	0.93	

Study Number	S-9	Solvent Control (Negative Control)		Historical Data Made On
		DMF		
		Mean	± SD	
Average	+	11.84	1.16	01-11-2012

APPENDIX NO.II (Contd.)

HISTORICAL DATA OF NUMBER OF HISTIDINE REVERTANT COLONIES

Test System : *Salmonella typhimurium*

Strain : TA 97a

Study Number	S-9	Untreated Control		Positive Control		Solvent Control (Negative Control)				Historical Data Made On
						Distilled Water		DMSO		
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	
Average	-	103.90	2.87	421.46	13.21	108.05	3.67	110.56	3.22	31-10-2013
17541	-	107.67	0.58	416.00	13.11	-	-	110.67	1.53	02-12-2013
	-	106.00	2.00	425.33	22.03	-	-	111.67	1.53	
17510	-	107.00	1.00	414.67	8.08	-	-	110.00	2.00	09-12-2013
	-	107.00	1.00	414.33	5.51	-	-	110.33	2.52	
17569	-	108.00	2.65	415.33	11.37	-	-	110.00	2.00	19-12-2013
	-	110.00	2.00	420.00	7.21	-	-	111.67	2.52	
17575	-	104.00	2.65	413.33	6.11	-	-	112.33	0.58	02-01-2014
	-	101.00	1.00	405.33	6.11	-	-	110.00	1.00	
17576	-	102.67	1.15	412.00	4.00	107.67	2.08	-	-	16-01-2014
	-	104.00	2.00	413.33	2.31	108.67	1.15	-	-	
17548	-	104.00	1.73	604.00	4.00	110.00	2.65	-	-	03-02-2014
	-	105.00	2.00	606.00	4.00	110.33	2.08	-	-	
17534	-	106.33	2.52	416.00	10.58	110.33	1.53	-	-	20-02-2014
	-	106.67	1.53	412.00	14.42	110.33	2.08	-	-	
17852	-	100.67	3.06	433.33	12.22	-	-	101.00	1.00	27-03-2014
	-	101.33	4.16	432.67	25.32	-	-	104.00	2.00	
17774	-	97.00	2.65	405.33	10.07	104.33	2.08	-	-	16-04-2014
	-	98.67	3.06	402.67	12.86	107.00	1.00	-	-	
17957	-	97.00	3.46	368.67	21.57	-	-	100.33	1.53	21-05-2014
	-	92.00	2.00	352.00	28.84	-	-	99.00	2.00	
17958	-	89.33	4.62	314.67	14.05	-	-	95.00	2.65	06-06-2014
	-	94.33	4.04	324.00	8.00	-	-	95.00	3.61	
Average	-	102.33	2.34	419.24	11.52	108.52	2.04	106.10	1.98	

Study Number	S-9	Solvent Control (Negative Control)		Historical Data Made On
		DMF		
		Mean	± SD	
Average	-	113.83	4.66	01-11-2012

APPENDIX NO.II (Contd.)

HISTORICAL DATA OF NUMBER OF HISTIDINE REVERTANT COLONIES

Test System : *Salmonella typhimurium*

Strain : TA 97a

Study Number	S-9	Untreated Control		Positive Control		Solvent Control (Negative Control)				Historical Data Made On
						Distilled Water		DMSO		
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	
Average	+	107.58	3.26	1185.10	24.57	113.13	3.15	112.34	3.50	31-10-2013
17541	+	109.67	2.08	1112.67	13.32	-	-	114.00	1.00	02-12-2013
	+	108.33	1.53	1102.67	18.90	-	-	113.67	1.53	
17510	+	109.33	2.52	1110.33	17.62	-	-	114.33	1.53	09-12-2013
	+	111.33	0.58	1114.00	25.24	-	-	115.33	1.53	
17569	+	111.33	2.52	1118.67	14.47	-	-	114.33	0.58	19-12-2013
	+	108.67	3.06	1112.67	13.61	-	-	114.67	3.06	
17575	+	107.00	2.65	1103.33	7.57	-	-	112.67	2.52	02-01-2014
	+	106.67	1.53	1093.33	8.33	-	-	112.00	1.00	
17576	+	107.33	1.15	1060.00	26.23	111.00	1.00	-	-	16-01-2014
	+	107.67	1.53	1058.67	16.17	111.33	1.53	-	-	
17548	+	111.33	3.21	1128.00	18.33	113.67	3.06	-	-	03-02-2014
	+	110.33	3.51	1124.00	19.70	111.33	3.06	-	-	
17534	+	109.33	1.15	1133.33	12.22	111.00	3.00	-	-	20-02-2014
	+	110.00	1.00	1128.67	16.29	112.00	2.65	-	-	
17852	+	104.67	2.08	1100.67	18.15	-	-	106.67	3.51	27-03-2014
	+	105.33	2.08	1088.67	18.58	-	-	105.00	3.61	
17774	+	99.33	5.03	1106.67	12.22	104.67	2.52	-	-	16-04-2014
	+	99.33	3.06	1109.33	12.06	105.67	3.51	-	-	
17957	+	100.33	1.53	1087.33	29.14	-	-	102.00	2.00	21-05-2014
	+	92.67	3.06	1093.33	32.08	-	-	103.67	4.04	
17958	+	90.00	2.00	1084.00	14.42	-	-	95.67	3.21	06-06-2014
	+	95.33	3.51	1076.00	12.00	-	-	102.00	2.00	
Average	+	105.34	2.33	1105.71	17.44	110.42	2.61	109.22	2.31	

Study Number	S-9	Solvent Control (Negative Control)		Historical Data Made On
		DMF		
		Mean	± SD	
Average	+	119.17	5.20	01-11-2012

APPENDIX NO.II (Contd.)

HISTORICAL DATA OF NUMBER OF HISTIDINE REVERTANT COLONIES

Test System : *Salmonella typhimurium*

Strain : TA 98

Study Number	S-9	Untreated Control		Positive Control		Solvent Control (Negative Control)				Historical Data Made On
						Distilled Water		DMSO		
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	
Average	-	26.66	1.31	369.45	23.43	29.55	1.15	28.02	1.38	31-10-2013
17541	-	24.67	1.15	314.67	6.43	-	-	25.33	2.52	02-12-2013
	-	24.67	1.15	312.00	17.44	-	-	25.33	2.52	
17510	-	26.00	2.00	312.67	6.43	-	-	26.00	2.00	09-12-2013
	-	27.00	1.00	314.00	2.00	-	-	27.00	1.00	
17569	-	27.67	0.58	312.00	5.29	-	-	26.33	2.08	19-12-2013
	-	27.33	2.08	314.67	10.07	-	-	26.67	2.08	
17575	-	23.67	1.53	316.00	18.33	-	-	24.33	1.15	02-01-2014
	-	23.33	2.08	334.67	43.14	-	-	23.33	1.53	
17576	-	23.33	0.58	314.67	10.07	24.67	0.58	-	-	16-01-2014
	-	23.33	1.15	316.00	16.00	26.00	1.00	-	-	
17548	-	23.33	1.15	316.00	16.00	26.00	1.00	-	-	03-02-2014
	-	22.00	1.00	321.33	12.86	22.33	1.53	-	-	
17534	-	23.67	1.53	326.00	15.10	24.00	1.00	-	-	20-02-2014
	-	23.00	1.00	318.67	16.17	24.67	1.53	-	-	
17852	-	23.00	1.00	319.33	12.06	-	-	24.00	2.00	27-03-2014
	-	22.67	1.15	317.33	18.04	-	-	22.67	0.58	
17774	-	24.67	2.08	305.33	8.33	26.67	1.53	-	-	16-04-2014
	-	22.33	0.58	311.33	19.43	24.00	1.00	-	-	
17957	-	21.33	1.53	325.33	10.07	-	-	24.00	2.00	21-05-2014
	-	24.00	2.00	328.00	18.33	-	-	25.67	0.58	
17958	-	22.00	1.00	317.33	6.11	-	-	25.33	3.21	06-06-2014
	-	23.00	1.00	309.33	8.33	-	-	24.00	1.00	
Average	-	24.03	1.29	319.40	13.89	25.32	1.15	25.20	1.71	

Study Number	S-9	Solvent Control (Negative Control)		Historical Data Made On
		DMF		
		Mean	± SD	
Average	-	30.00	1.81	01-11-2012

APPENDIX NO.II (Contd.)

HISTORICAL DATA OF NUMBER OF HISTIDINE REVERTANT COLONIES

Test System : *Salmonella typhimurium*

Strain : TA 98

Study Number	S-9	Untreated Control		Positive Control		Solvent Control (Negative Control)				Historical Data Made On
						Distilled Water		DMSO		
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	
Average	+	28.29	1.57	1171.57	31.90	31.55	1.52	29.19	1.21	31-10-2013
17541	+	25.33	1.53	1086.67	12.22	-	-	28.00	1.00	02-12-2013
	+	28.00	1.00	1078.00	13.11	-	-	28.00	1.00	
17510	+	28.00	1.00	1086.00	18.33	-	-	28.67	0.58	09-12-2013
	+	28.00	1.00	1083.33	14.47	-	-	28.00	1.00	
17569	+	28.33	3.06	1100.00	17.44	-	-	29.00	1.00	19-12-2013
	+	27.33	2.08	1108.00	12.49	-	-	29.00	2.00	
17575	+	24.00	1.00	1124.67	44.38	-	-	24.67	2.08	02-01-2014
	+	23.67	0.58	1109.33	31.07	-	-	23.67	1.15	
17576	+	26.67	0.58	1024.00	14.42	30.33	4.93	-	-	16-01-2014
	+	25.67	0.58	1019.33	9.45	27.00	1.73	-	-	
17548	+	25.67	0.58	1026.00	8.72	27.00	1.73	-	-	03-02-2014
	+	24.67	1.15	1014.67	12.86	27.00	1.00	-	-	
17534	+	25.00	1.00	1050.00	15.87	27.00	1.00	-	-	20-02-2014
	+	25.33	0.58	1038.67	16.17	27.33	0.58	-	-	
17852	+	23.67	1.53	1104.67	13.01	-	-	24.33	1.53	27-03-2014
	+	23.00	1.00	1082.67	52.20	-	-	23.67	1.53	
17774	+	25.67	0.58	1081.33	54.45	27.00	1.73	-	-	16-04-2014
	+	25.33	0.58	1073.33	40.07	27.33	0.58	-	-	
17957	+	24.33	2.52	1058.67	37.17	-	-	26.00	1.73	21-05-2014
	+	25.33	2.08	1030.67	14.05	-	-	25.67	1.53	
17958	+	23.33	0.58	1017.33	14.05	-	-	24.33	0.58	06-06-2014
	+	24.33	0.58	1028.00	14.42	-	-	25.33	0.58	
Average	+	25.61	1.16	1069.43	22.27	27.95	1.64	26.50	1.23	

Study Number	S-9	Solvent Control (Negative Control)		Historical Data Made On
		DMF		
		Mean	± SD	
Average	+	30.67	1.29	01-11-2012

APPENDIX NO.II (Contd.)

HISTORICAL DATA OF NUMBER OF HISTIDINE REVERTANT COLONIES

Test System : *Salmonella typhimurium*

Strain : TA 100

Study Number	S-9	Untreated Control		Positive Control		Solvent Control (Negative Control)				Historical Data Made On
						Distilled Water		DMSO		
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	
Average	-	105.89	2.79	638.51	14.62	110.72	2.60	109.93	3.61	31-10-2013
17541	-	103.33	1.53	609.33	8.33	-	-	109.67	1.53	02-12-2013
	-	106.33	2.08	624.00	12.00	-	-	110.33	1.53	
17510	-	104.67	1.53	625.33	12.22	-	-	110.00	1.73	09-12-2013
	-	106.33	2.08	627.33	18.90	-	-	109.33	1.53	
17569	-	107.67	1.15	623.33	7.57	-	-	111.33	1.53	19-12-2013
	-	107.67	2.08	626.67	13.32	-	-	108.67	2.08	
17575	-	108.67	2.52	622.00	11.14	-	-	109.67	6.66	02-01-2014
	-	108.33	3.21	618.67	18.04	-	-	111.33	4.16	
17576	-	106.00	2.00	616.67	7.02	112.33	3.79	-	-	16-01-2014
	-	107.67	1.15	428.00	4.00	110.00	2.65	-	-	
17548	-	106.33	0.58	413.33	12.22	107.33	0.58	-	-	03-02-2014
	-	107.67	1.15	413.33	12.22	109.00	1.00	-	-	
17534	-	102.67	2.52	610.67	7.02	109.67	2.52	-	-	20-02-2014
	-	104.00	3.00	607.33	14.74	109.00	1.00	-	-	
17852	-	103.33	1.15	574.00	10.00	-	-	109.67	2.08	27-03-2014
	-	108.00	2.00	574.67	7.02	-	-	108.67	2.89	
17774	-	106.00	2.00	517.33	12.22	105.33	2.08	-	-	16-04-2014
	-	107.00	2.65	421.33	12.22	105.67	2.08	-	-	
17957	-	99.00	3.61	425.33	10.07	-	-	103.67	1.53	21-05-2014
	-	95.00	5.00	425.33	10.07	-	-	103.67	2.08	
17958	-	99.33	1.15	417.33	7.57	-	-	105.67	1.53	06-06-2014
	-	100.00	2.00	417.33	14.05	-	-	105.33	1.53	
Average	-	104.82	2.13	542.48	11.16	108.78	2.03	108.46	2.40	

Study Number	S-9	Solvent Control (Negative Control)		Historical Data Made On
		DMF		
		Mean	± SD	
Average	-	115.84	2.26	01-11-2012

APPENDIX NO.II (Contd.)

HISTORICAL DATA OF NUMBER OF HISTIDINE REVERTANT COLONIES

Test System : *Salmonella typhimurium*

Strain : TA 100

Study Number	S-9	Untreated Control		Positive Control		Solvent Control (Negative Control)				Historical Data Made On
						Distilled Water		DMSO		
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	
Average	+	110.72	2.85	1242.66	30.71	116.04	3.58	112.30	3.57	31-10-2013
17541	+	107.67	2.52	1154.67	25.72	-	-	111.33	2.08	02-12-2013
	+	108.00	3.61	1148.00	26.23	-	-	111.00	2.00	
17510	+	110.33	3.06	1163.33	28.02	-	-	111.33	2.08	09-12-2013
	+	108.67	2.52	1168.00	22.00	-	-	110.67	2.52	
17569	+	111.00	1.73	1159.33	28.02	-	-	111.33	2.08	19-12-2013
	+	109.00	1.73	1170.00	28.84	-	-	111.67	2.52	
17575	+	108.67	1.15	1164.00	20.00	-	-	110.00	4.00	02-01-2014
	+	108.00	4.58	1154.67	19.01	-	-	111.33	3.06	
17576	+	108.33	2.08	1142.67	22.03	113.00	5.29	-	-	16-01-2014
	+	109.00	1.00	1057.33	20.13	112.33	3.79	-	-	
17548	+	110.67	1.53	1057.33	22.74	114.00	1.00	-	-	03-02-2014
	+	109.67	2.52	1044.00	21.17	111.33	1.15	-	-	
17534	+	107.67	1.53	1154.00	13.11	112.00	2.00	-	-	20-02-2014
	+	107.67	2.52	1138.67	16.17	112.67	1.53	-	-	
17852	+	103.67	1.53	1143.33	12.06	-	-	110.67	1.15	27-03-2014
	+	107.67	1.53	1138.00	14.00	-	-	109.33	1.15	
17774	+	107.00	3.61	1106.67	12.22	110.67	2.31	-	-	16-04-2014
	+	107.67	4.51	1109.33	12.06	109.00	1.00	-	-	
17957	+	104.00	2.00	1101.33	16.65	-	-	105.33	3.79	21-05-2014
	+	102.33	2.52	1101.33	16.65	-	-	107.00	1.73	
17958	+	105.00	1.00	1140.00	53.70	-	-	105.67	1.15	06-06-2014
	+	105.33	3.06	1104.00	98.06	-	-	106.67	1.15	
Average	+	107.73	2.38	1133.16	25.19	112.34	2.41	109.71	2.27	

Study Number	S-9	Solvent Control (Negative Control)		Historical Data Made On
		DMF		
		Mean	± SD	
Average	+	119.00	2.00	01-11-2012

APPENDIX NO.II (Contd.)

HISTORICAL DATA OF NUMBER OF HISTIDINE REVERTANT COLONIES

Test System : *Salmonella typhimurium*

Strain : TA 102

Study Number	S-9	Untreated Control		Positive Control		Solvent Control (Negative Control)				Historical Data Made On
						Distilled Water		DMSO		
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	
Average	-	272.52	9.24	3607.28	157.31	273.39	10.37	290.08	11.02	31-10-2013
17541	-	262.67	10.07	2688.00	35.55	-	-	270.67	10.07	02-12-2013
	-	260.00	20.00	2694.67	24.44	-	-	275.33	10.26	
17510	-	256.67	8.08	2763.67	49.64	-	-	263.33	13.32	09-12-2013
	-	264.67	18.15	2750.00	75.45	-	-	264.67	18.15	
17569	-	279.33	15.01	2796.00	13.11	-	-	272.00	15.87	19-12-2013
	-	274.67	4.16	2766.00	51.42	-	-	271.33	13.32	
17575	-	220.00	3.46	2629.33	112.59	-	-	248.67	21.01	02-01-2014
	-	222.00	7.21	3014.67	6.11	-	-	222.00	7.21	
17576	-	220.67	4.16	3016.00	4.00	226.67	3.06	-	-	16-01-2014
	-	212.00	6.93	3021.33	6.11	228.00	4.00	-	-	
17548	-	208.67	8.08	3013.33	12.22	210.67	10.07	-	-	03-02-2014
	-	211.33	5.03	3024.67	8.08	224.00	4.00	-	-	
17534	-	255.33	11.02	2746.67	72.59	260.67	18.15	-	-	20-02-2014
	-	256.67	8.08	2716.67	61.33	275.33	8.33	-	-	
17852	-	255.33	5.03	2738.67	70.47	-	-	261.33	4.62	27-03-2014
	-	288.00	6.00	2754.00	56.32	-	-	288.00	4.00	
17774	-	266.67	5.03	2742.67	65.03	270.67	8.08	-	-	16-04-2014
	-	271.33	7.02	2737.33	66.64	289.33	4.16	-	-	
17957	-	258.67	4.62	2613.33	108.39	-	-	268.67	5.03	21-05-2014
	-	229.33	4.62	2468.67	65.43	-	-	244.67	14.19	
17958	-	276.00	17.44	2328.67	98.19	-	-	321.33	4.62	06-06-2014
	-	281.33	16.17	2408.00	31.75	-	-	324.00	12.00	
Average	-	252.34	8.90	2784.33	54.44	250.97	7.80	272.41	10.98	

Study Number	S-9	Solvent Control (Negative Control)		Historical Data Made On
		DMF		
		Mean	± SD	
Average	-	314.34	10.80	01-11-2012

APPENDIX NO.II (Contd.)

HISTORICAL DATA OF NUMBER OF HISTIDINE REVERTANT COLONIES

Test System : *Salmonella typhimurium*

Strain : TA 102

Study Number	S-9	Untreated Control		Positive Control		Solvent Control (Negative Control)				Historical Data Made On
						Distilled Water		DMSO		
		Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD	
Average	+	280.20	11.67	1193.74	26.39	282.84	8.51	297.53	10.31	31-10-2013
17541	+	261.33	16.65	1040.00	34.18	-	-	278.67	5.03	02-12-2013
	+	276.00	31.24	1034.67	25.72	-	-	292.00	5.29	
17510	+	265.33	12.22	1044.00	38.63	-	-	276.00	12.17	09-12-2013
	+	279.33	10.26	1040.67	32.02	-	-	278.67	12.86	
17569	+	272.00	13.11	1044.00	34.12	-	-	280.00	7.21	19-12-2013
	+	281.33	6.11	1028.00	14.42	-	-	273.33	13.61	
17575	+	234.00	7.21	1025.33	10.07	-	-	248.67	17.47	02-01-2014
	+	222.00	9.17	1178.00	13.11	-	-	222.00	9.17	
17576	+	222.67	2.31	1161.33	16.17	230.00	4.00	-	-	16-01-2014
	+	230.67	4.62	1166.00	8.00	231.33	4.16	-	-	
17548	+	226.00	5.29	1159.33	5.03	226.00	5.29	-	-	03-02-2014
	+	226.00	5.29	1134.67	32.33	232.67	3.06	-	-	
17534	-	255.33	11.02	2746.67	72.59	260.67	18.15	-	-	20-02-2014
	-	256.67	8.08	2716.67	61.33	275.33	8.33	-	-	
17852	+	268.00	6.93	1040.00	18.33	-	-	277.33	10.07	27-03-2014
	+	288.67	5.03	1042.67	8.33	-	-	289.33	4.16	
17774	+	270.67	6.43	1043.33	11.02	274.67	7.02	-	-	16-04-2014
	+	275.33	6.11	1043.33	13.32	291.33	4.16	-	-	
17957	+	266.00	11.14	1036.00	20.00	-	-	276.67	11.37	21-05-2014
	+	228.67	6.43	1030.67	14.05	-	-	257.33	15.14	
17958	+	294.00	4.00	1023.33	11.72	-	-	332.00	14.42	06-06-2014
	+	291.33	4.16	1024.00	12.00	-	-	332.00	17.44	
Average	+	259.63	8.89	1217.24	23.17	256.09	6.96	280.77	11.05	

Study Number	S-9	Solvent Control (Negative Control)		Historical Data Made On
		DMF		
		Mean	± SD	
Average	+	322.67	6.51	01-11-2012

APPENDIX NO.III

CHARACTERIZATION OF *SALMONELLA* STRAINS

Test System : *Salmonella typhimurium*

Genotype Characteristic	TA 1535	TA 97a	TA 98	TA 100	TA 102
Histidine Requirement					
Histidine -	-	-	-	-	-
Histidine +	+	+	+	+	+
R - Factor					
Ampicillin +	-	+	+	+	+
rfa mutation					
Zone of Inhibition (mm)	16	15	18	19	16
UVrB - mutation					
UV irradiated	-	-	-	-	-
UV non-irradiated	+	+	+	+	-
PAQ1 plasmid					
Ampicillin $^{+}$ + Tetracycline^{+}	-	-	-	-	+
Mean Spontaneous Revertants	11.5	98.4	32.0	112.0	261.0

ANNEXURE - I

Certificate of Analysis (1 Page)

advanced enzymes
Where ENZYME is Life

Advanced Enzyme Technologies Ltd.,
Plot No. A-61/62, MIDC, Malegaon, Tal. Sinnar, Dist. Nashik - 422 113,
Maharashtra, India. Tel.: +91-99701 00750 / +91-2551-230 044, Fax: +91-2551-230 816
Email: info@enzymeindia.com, Web.: www.enzymeindia.com

QUALITY ASSURANCE DEPARTMENT

CERTIFICATE OF ANALYSIS

PRODUCT NAME : RHIZOPUS LIPASE
BATCH NO. : 011423
MFG. DATE : JANUARY,2014
EXPIRY DATE : DECEMBER,2015

PROTOCOL OF ANALYSIS

TEST	RESULT	LIMITS
Description	Light Brown coloured amorphous, hygroscopic powder; having typical fermentative odour	Light Brown to Brown coloured amorphous, hygroscopic powder; having typical fermentative odour
Solubility	Soluble in Water **: Complies**	Soluble in Water.
Lead	**: Complies**	Not more than 5 ppm
Microbial Limit- **Total viable count** **Total coliforms/g** **Escherichia.coli/25g** **Salmonellae/25g**	 **: Complies** **: Complies** **: Complies** **: Complies**	 NMT 1 x 10^4 cfu/g Not more than 30 Negative by test Negative by test
Antimicrobial Activity	Absent by test **: Complies**	Absent by test
Rhizopus Lipase Activity	548,964 FIP U/g	NLT 500,000 FIP U/g

Remarks: Sample **COMPLIES** as per Specifications.

(b) (6)

QA-CHEMIST
Date: February 1, 2014

(b) (6)

MANAGER-QUALITY ASSURANCE

ANNEXURE - II

Certificate of Approval
(Good Laboratory Practice, GLP)
(1 Page)

सत्यमेव जयते

NATIONAL GLP COMPLIANCE MONITORING AUTHORITY

GLP CERTIFICATE

GLP Inspection was carried out at **Indian Institute of Toxicology, 32 A/1, Hadapsar Industrial Estate, Pune – 411013, Maharashtra, INDIA** in the following areas of expertise:

- **Toxicity studies**
  - Acute Studies (Oral, Parenteral, Dermal, Inhalation, Dermal Irritation/ Corrosion, Eye Irritation/ Corrosion, Skin Sensitization Test)
  - Sub-acute Studies
  - Chronic Studies
- **Mutagenicity Studies**
  - Bacterial Reverse Mutation Assay (Ames Test)
  - Mammalian Erythrocyte Micronucleus Test
  - *In vivo/ In Vitro* Mammalian Chromosome Aberration Test

Based on the Inspection Report and the follow-up actions taken by the test facility, it is confirmed that the test facility is capable of conducting the above-mentioned tests/studies in compliance with OECD Principles of Good Laboratory Practice (GLP) for the types of chemicals and in test systems as listed below respectively:

Types of chemicals	:	Industrial Chemicals, Pesticides, Pharmaceuticals, Veterinary Drugs, Cosmetics, Food additives and Feed additives
Test Systems	:	Rat, Mice, Guinea pig, Rabbit, *Salmonella typhimurium,* tester strains viz. (TA 97a, TA 98, TA 100, TA 1535 & TA 102)

This GLP Certificate is valid for a period of three years from April 16, 2013, subject to the condition that the test facility complies with the Terms & Conditions of the National GLP Compliance Monitoring Authority's Document Number GLP-101.

(b) (6)

Certificate No. : GLP/C-046

Issue Date : 10-04-2013

(VINITA SHARMA)
Head
National GLP Compliance Monitoring Authority
Department of Science & Technology
Technology Bhavan New Delhi-110016

ANNEXURE - III

Summary of Amendment(s) to the Study Plan (1 Page)

Summary of Amendment(s) to the Study Plan

Amendment Number	Amendment
1	Study Completion Date finalized.

INDIAN INSTITUTE OF TOXICOLOGY

भारतीय विषविज्ञान संस्था

FOUNDER DIRECTOR Late. DR. M. B. BHIDE (M.D.,F.C.A.I.)
Registered Office : "Kim" 2057, Sadashiv Peth, Pune - 411 030.
Correspondance Office : Flat No. 301, 401 "Usha-Shree" 90/124C, Erandawane, Gangote Street,
Near Kamala Nehru Park, Pune - 411004.
Tel. Fax : (Testing Facility) : 020 - 2681 9961, 020 - 2681 9962 E-mail : iitoxicology@gmail.com

FINAL REPORT

(AMENDED ON 09-09-2016)

IIT STUDY NUMBER 17783

IN VITRO MAMMALIAN CHROMOSOME ABERRATION TEST OF RHIZOPUS LIPASE IN HUMAN LYMPHOCYTES

STUDY DIRECTOR
DR. (MRS.) R.P.DIGHE Ph.D.

TESTING FACILITY :
INDIAN INSTITUTE OF TOXICOLOGY
32 A/1, Hadapsar Industrial Estate,
Pune - 411 013.

SPONSOR'S REPRESENTATIVE
Mrs. Shilpa Risbud

SPONSOR ADDRESS :
ADVANCED ENZYME TECHNOLOGIES LTD.,
Sun Magnetica, 'A' wing, 5th Floor,
LIC Service Road,
Louiswadi, Thane (W) 400 604
Maharashtra, India.

REGULATORY REQUIREMENTS:

OECD guidelines for testing of chemicals section 4, *In vitro* Mammalian Chromosome Aberration Test, Test No.473 Adopted on 26th September 2014.

CONFIDENTIAL

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STATEMENT OF GLP COMPLIANCE

Title of the Study	: *In Vitro* Mammalian Chromosome Aberration Test of Rhizopus Lipase in Human Lymphocytes
Study Number	: 17783
Study Plan Number	: SPL/002/053
Name of the Test item	: Rhizopus Lipase

The study was conducted in accordance with the Good Laboratory Practice Principles as Published by the OECD in 1998, No 1 ENV/MC/CHEM(98)17.

Mr. V.M.Bhide M.B.A.	(b) (6)	09.09.2016
Test Facility Management	Signature	Date

STATEMENT OF COMPLIANCE WITH GOOD LABORATORY PRACTICE

Title of the Study	: *In Vitro* Mammalian Chromosome Aberration Test of Rhizopus Lipase in Human Lymphocytes
Study Number	: 17783
Study Plan Number	: SPL/002/053
Name of the Test item	: Rhizopus Lipase

The study was conducted in compliance to the Good Laboratory Principles as Published by OECD in 1998, No 1 ENV/MC/CHEM(98)17.

The study was conducted in compliance to the written Study Plan approved by the Study Director and authorized by the Sponsor and Indian Institute of Toxicology Management and all applicable Standard Operating Procedures of Indian Institute of Toxicology, Pune.

All original Raw Data including documentation, slides generated during the course of the study, signed Study Plan, Study Plan Amendments and a copy of final report are archived at Indian Institute of Toxicology, Pune.

I accept responsibility for the conduct of the study and hereby declare that the study was conducted under my direction. This report is a complete, true and accurate record of the results obtained.

This report is amended for correction in duration of exposure for main experiment as per raw data.

The sponsor is responsible for Good laboratory Practice (GLP) compliance for all test item information such as test item characterization, test item stability and Material Safety Data Sheet (MSDS) provided to test facility.

Dr. (Mrs.) R.P.Dighe Ph.D.	(b) (6)	09/09/2016
Study Director	Signature	Date

STATEMENT OF QUALITY ASSURANCE UNIT

Title of the Study : *In Vitro* Mammalian Chromosome Aberration Test of Rhizopus Lipase in Human Lymphocytes

Study Number : 17783

Study Plan Number : SPL/002/053

Name of the Test item : Rhizopus Lipase

This study has been audited and the final report has been examined with respect to study plan, SOP and raw data. The report is true reflection of the raw data and that the study was conducted in compliance with the principles of GLP. The audits were carried out according to the applicable SOP's of Quality Assurance Unit of Indian Institute of Toxicology, Pune. The report is kept in the archives at Indian Institute of Toxicology, Pune.

Inspections were made by the Quality Assurance Unit of the Indian Institute of Toxicology for different phases of the study described in this report. The dates on which the inspections were made and the dates on which the findings were reported to the Study Director and to the facility Management are given below.

Date(s) of Inspection	Phases Inspected	Date(s) findings reported to Study Director	Date(s) findings reported to Management
12/02/2014	Study Plan Review	12/02/2014	12/02/2014
24/09/2014	Pre Study Verification	24/09/2014	24/09/2014
24/09/2014	Amendment - 1	24/09/2014	24/09/2014
27/09/2014	Maintenance and Storage of Test System	27/09/2014	27/09/2014
10/10/2014	Harvesting of Cell Cultures	10/10/2014	10/10/2014
15/11/2014	Raw Data Audit	15/11/2014	15/11/2014
17/11/2014	Draft Report Audit	17/11/2014	17/11/2014
12/12/2014	Amendment – 2	12/12/2014	12/12/2014
15/12/2014	Final Report Audit	15/12/2014	15/12/2014
09/09/2016	Amended Final Report Review	09/09/2016	09/09/2016

Mrs. C.S.Bhide M.Sc. (b) (6) 9.9.2016

Quality Assurance Unit Signature Date

PERSONNEL INVOLVED IN THE STUDY

Study Director	: Dr. R.P.Dighe Ph.D.
Study Scientist	: Mr. A.B.Sarvadnya M.Sc.
Statistics	: Mr. S.D.Nagpure B.Com. Mr. D.K.Raut H.S.C.
Quality Assurance Unit	: Dr. P.R.Tikhe Ph.D. Dr. R.M.Gosavi M.V.Sc. Mrs. C.S.Bhide M.Sc.
Report Preparation	: Dr. R.P.Dighe Ph.D. Mr. S.D.Nagpure B.Com.

LIST OF ABBREVIATIONS

IIT	-	Indian Institute of Toxicology
GLP	-	Good Laboratory Practice
OECD	-	Organization for Economic Co-operation and Development
SOP	-	Standard Operating Procedure
mg	-	Milligram
µg	-	Microgram
µL	-	Microliter
°C	-	Degree Celsius
%	-	Percent
No.	-	Number
Nos.	-	Numbers
ml	-	Milliliter
S9	-	Supernatant at 9000 g
EMS	-	Ethyl methanesulphonate
Conc.	-	Concentration

SUMMARY AND CONCLUSION

The present study was conducted to evaluate the clastogenic potential of **Rhizopus Lipase**.

Human Lymphocyte cultures were set and incubated at 37°C for 48 hours. The test item did not precipitate in Eagle's Minimum Essential Medium (MEM) at and up to 5 mg/ml of culture. Therefore, cytotoxicity was conducted at test item concentration(s) of 5 mg/ml of culture, 2.5 mg/ml of culture, 1.25 mg/ml of culture, 0.625 mg/ml of culture and 0.312 mg/ml of culture using mitotic index as an indicator of cytotoxicity.

Evaluation of mitotic index indicated that the test item did not inhibit mitotic activity at 5.0 mg/ml of culture and therefore the test item was not cytotoxic at the concentration of 5 mg/ml of culture. The reduction in mitotic activity was 0.98% to 2.22% at 5.0 mg/ml of culture. Therefore, the highest concentration selected for the main study was 5 mg/ml of culture and subsequent two lower concentrations selected were 2.5 mg/ml of culture and 1.25 mg/ml of culture.

Human Lymphocyte cultures were set and incubated at 37°C for 48 hours.

In first set, cultures with and without S9 were exposed to the test item for 4 hours at 5 mg/ml of culture, 2.5 mg/ml of culture and 1.25 mg/ml of culture concentration followed by change of the medium.

Untreated cultures, cultures exposed to solvent distilled water and cultures exposed to positive control were run simultaneously.

In the second set, cultures with S9 were exposed to test item for 4 hours at 5 mg/ml of culture, 2.5 mg/ml of culture and 1.25 mg/ml of culture followed by change of the medium.

Cultures without S9 were exposed to test item for 24 hours at 5 mg/ml of culture, 2.5 mg/ml of culture and 1.25 mg/ml of culture.

Untreated cultures, cultures exposed to solvent and cultures exposed to positive control were run simultaneously.

All cultures were incubated at 37°C for 24 hours after exposure to the test item. Three hours prior to harvesting, cultures were treated with colchicine to arrest the cell cycle at metaphase.

Harvested cultures were centrifuged, treated with hypotonic solution, fixed with fixative (1:3 acetic acid : methanol) and centrifuged. The slides of the cells obtained were prepared and stained with Giemsa. Three hundred metaphases were scored at each test point for chromosomal break analysis.

The test item did not induce increased chromosomal aberrations at and up to the highest concentration of 5 mg/ml of culture in comparison with solvent control.

Based on these results it is concluded that **Rhizopus Lipase** supplied by **Advanced Enzyme Technologies Ltd., Thane,** tested at and up to 5 mg/ml of culture concentration did not induce chromosome aberrations in human lymphocyte cells *in vitro* and is therefore non-clastogenic in the presence and absence of microsomal enzymes (S-9 fraction).

(b) (6)

Dr. (Mrs.) R.P.Dighe
Study Director

1) The results relate only to the items tested.
2) This report shall not be reproduced except in full, without the written approval of the laboratory.

Schedule

Study Initiation Date	: 12-02-2014
Range Finding Study	
Experimental Starting Date	: 27-09-2014
Main Study	
Experimental Starting Date	: 07-10-2014
Experiment Completion Date	: 10-11-2014
Study Completion Date	: 15-12-2014
Date of Reporting	: 15-12-2014
Final Report Amendment Date	: 09-09-2016

Archives

All original raw data, slides generated during the course of the study, the signed study plan, study plan amendments and a copy of final report is retained in the Archives of Indian Institute of Toxicology, Pune for a period of nine years. At the end of this period, the sponsor's instructions will be sought to either extend the archiving period or return the archived material to the sponsor or for the material to be disposed off.

Test Item Return

On completion of the study and submission of the final report, all unused samples of the test item was returned to the Sponsor.

Animal Welfare

No animal was used in this study.

OBJECTIVES

Purpose

The purpose of this study was to evaluate the **Rhizopus Lipase** and/or its metabolites for their ability to induce chromosomal aberrations in mammalian cells *in vitro* in the presence and absence of mammalian microsomal enzymes (S9).

MATERIALS AND METHODS

Test Item

Sponsor	: **Advanced Enzyme Technologies Ltd., Thane**
Laboratory Sponsor Code	: **SPN/002**
Test Item	: **Rhizopus Lipase**
Batch Number	: **011423**
Laboratory Test Item Code	: **TAS/002/015**
Manufacturing Date	: **January, 2014**
Expiry Date	: **December, 2015**
Consistency	: **Solid powder**
Activity (Clinical Indication)	: **Food Enzyme**
Safety Precautions	: Safety precautions included use of protective clothing, gloves, masks and eye protection (glasses).
Stability Data	: Information on file with the Sponsor.
Storage Condition	: Ambient temperature
Dose Preparation	: Test item was dissolved in distilled water and diluted to required concentrations prior to exposure of cell cultures. Actual preparation procedures are documented in the raw data.
Solvent	: Distilled water

Disclaimer :

The above physiochemical data of test substance is supplied by the Sponsor. All responsibility with regards to the accuracy and authenticity of this information remains with the Sponsor. The test lab is not responsible for any variations with the batch number supplied.

Test System

Mammalian cells *in vitro*: Human Lymphocyte cell cultures

Source: A healthy human volunteer.
Lymphocytes from different individuals may respond differently to culture conditions or the test materials. Therefore, lymphocytes from only one healthy donor was used in the study.

Characteristics: Modal chromosome number (2n = 46)

Rationale for selection of Human Lymphocytes cell cultures:

Human Lymphocyte cell culture is the appropriate test system because the evaluation of data can be directly related to human beings.

Study Design

Culture Conditions:

Appropriate culture media and incubation conditions (culture vessels, CO_2 concentration, temperature and humidity) were used to maintain cultures. The cultures were monitored routinely for the absence of mycoplasma contamination and were not used if contaminated.
The normal cell cycle time for the cells and culture conditions used was pre-known.

Following culture media were used in the test:

Minimum essential medium (Hi media) supplemented with 10% Fetal Bovine Serum (FBS) to grow cell cultures, mitogen (phytohemagglutinin) to induce mitosis, anticoagulant (heparin) used to avoid clotting of blood, S9 mix (with metabolic activation) / phosphate buffer (without metabolic activation).

The following volumes were added to the culture vessel:

9.25 ml culture media containing 10% v/v FBS
0.4 ml heparinized whole blood
0.25 ml Phytohaemagglutinin
0.1 ml antibiotic solution
Total Volume (10 ml)

All the incubations were done at 37 °C.

Incubation Period: 72 hours

Number of cultures:

Duplicate cultures (with and without metabolic activation) were maintained at each concentration of test item, solvent control (negative control), untreated control and positive control. Total number of cultures maintained were 44 in number.

Metabolic activation:

Liver Homogenate S9 Fraction:

The Liver Homogenate S9 Fraction was available (preparation date 29-04-2014, batch number 12). The total proteins analysis was conducted and activity was evaluated and was found to be 41.2 mg/ml (acceptable range 35 - 45 mg/ml).
The S-9 mix was prepared immediately prior to its use in the assay. The microsomal reaction mixture (S-9 mix) contained the following components (D.M.Maron and B.N.Ames, (1983).
For 20 ml

1) S9 fraction	2.00 ml
2) 0.4 M MgCl2-0.65 M KCl salt solution	0.40 ml
3) 1.0 M G-6-P	0.20 ml
4) 0.4 mM NADP	0.20 ml
5) 0.2 M Phosphate buffer pH 7.4	17.20 ml

Experimental Design:

Control Items:

Untreated controls with and without microsomal enzymes were used in the study.

Solvent controls (negative control): Distilled water with and without microsomal enzymes were employed in the study.

Positive Controls:

Ethyl methane sulphonate (EMS) at concentration of 120 µg per ml of culture was used without metabolic activation.

Benzo(a) pyrene at concentration of 0.2 µg per ml of culture was used with metabolic activation.

Cytotoxicity Study:

Cytotoxicity was conducted at five different concentrations of the test item using mitotic index as an indicator of cytotoxicity. The highest concentration was 5 mg/ml of culture. Four lower concentrations in the multiple of two were tested. Negative control (solvent used) was employed along with test concentrations.

Selection of Concentrations for Main Study:

Based on the results of the cytotoxicity study, the concentrations for main study were finalized. Evaluation of mitotic index indicated that the test item did not inhibit mitotic activity at 5.0 mg/ml of culture and therefore the test item was not cytotoxic at the concentration of 5 mg/ml of culture. The reduction in mitotic activity was 0.98% to 2.22% at 5.0 mg/ml of culture. Therefore, the highest concentration selected for the main study was 5 mg/ml of culture and subsequent two lower concentrations selected were 2.5 mg/ml of culture and 1.25 mg/ml of culture.

Main Study:

Performance of the Test:

Cultures of heparinized whole blood were induced with mitogen (PHA) were set at 37 °C for 48 hours. The set cultures were then exposed to 3 concentrations of the test item.

The cultures thus obtained were divided into two sets i.e. Set I and Set II.

Set I:

Cultures were exposed to the test item with and without S9 for 4 hours. Cells were washed followed by change of the medium.

Untreated cultures, cultures exposed to solvent and cultures exposed to positive control were run simultaneously.

Set II:

Cultures with S9 were exposed to test item for 4 hours followed by change of the medium.

Cultures without S9 were exposed to test item for 24 hours.

Untreated cultures, cultures exposed to solvent and cultures exposed to positive control were run simultaneously.

Positive Controls:

Positive control included in set I was with metabolic activation for 4 hours of exposure.

Positive control included in set II was without metabolic activation for 24 hours of exposure.

Set I and Set II:

All cultures were incubated at 37°C for 24 hours after the exposure of test item.

The cultures were treated with colchicine three hours prior to harvesting to arrest the cell cycle at metaphase and centrifuged at approximately 1200 rpm for 10 minutes. The harvested cultures were then treated with hypotonic solution followed by centrifugation and were fixed with fixative (1:3 acetic acid : methanol). The slides of the cells obtained were prepared and stained with Giemsa.

Scoring of slides:

Three hundred metaphases were scored at each test point for chromosomal break analysis.

Type of Frequency of Aberrations and Observations:

Cytotoxicity: Slides were scanned for cytotoxicity and evaluated for mitotic index. The metaphases were scored for chromatid and chromosome aberrations. In addition, gaps and abnormalities such as endoreduplication, polyploidy were recorded. Gaps, endoreduplication, polyploidy were not part of the final score of chromosome aberrations and were not considered as aberrations in the final scoring to conclude mutagenic potential of test item.

For each concentration, 300 metaphases were analyzed for structural aberrations.

For Mitotic Index 2000 cells were counted and percentage was calculated.

All the slides were coded before the analysis and decoded after the analysis.

Mitotic Index was calculated as follows:

$$\text{Mitotic Index} = \frac{\text{Total number of cells in division}}{\text{Total number of cells counted}} \times 100$$

Data Analysis: (Table No.III, IV, V and VI)

Total number of aberrations per cell, percent of cells aberrated was analysed for statistical significance using student 't' test.

Acceptance Criteria: (Table No.III, IV, V, VI and Appendix No.I and II)

The assay was considered valid if the following criteria were met:

1) Slides to be assessed for aberrations should not have any evidence of contamination.
2) Mitotic index and percent aberrant cells in negative control cultures should normally be within or close to historical background data for these controls.
3) The binominal dispersion test demonstrates acceptable heterogeneity between replicate cultures.
4) The proportion of cells with structural chromosome aberration (excluding gaps) in negative control cultures falls within the calculated normal range.
5) The positive control chemicals induce statistically significant increases in the proportion of cells with structural chromosome aberrations.

Evaluation and Interpretation of Results:

The test item was considered as positive clastogen if it meets the following criteria:

1) The proportion of cells with structural chromosome aberrations at one or more concentration exceeds the calculated normal range in both replicate cultures.

2) A statistical significant increase in the proportion of cells with structural chromosome aberrations (excluding gaps, endoreduplication, polyploidy).

RESULTS

Mitotic Index (Table No.I and II)

Cytotoxicity Assay:

Set I :

Reduction in mitotic activity without and with metabolic activation at up to 5.0 mg/ml of culture ranged between 0.0% and 3.67%.

Set II :

Reduction in mitotic activity without and with metabolic activation up to 5.0 mg/ml of culture ranged between -1.0% and 1.0%.

Chromosome Break Analysis

Set I (4 hours exposure)
Without metabolic activation (Table No.III)

The number of chromosome aberrations per cell was 0.01, 0.01 and 0.007 at 5 mg/ml of culture, 2.5 mg/ml of culture and 1.25 mg/ml of culture concentrations. The number of chromosome aberrations per cell was 0.0 and 0.003 in untreated and solvent control group. The percent cells aberrated were 1.0, 1.0, 0.7 at 5 mg/ml of culture, 2.5 mg/ml of culture and 1.25 mg/ml of culture concentrations. The percent cells aberrated were 0.0 and 0.3 in untreated, solvent control group. The aberrations induced were of chromatid type only. Gaps were not considered in calculation of total aberrations in cells.

Chromosome Break Analysis

Set I (4 hours exposure)
With metabolic activation (Table No.IV)

The number of chromosome aberrations per cell was 0.01, 0.007 and 0.003 at 5 mg/ml of culture, 2.5 mg/ml of culture and 1.25 mg/ml of culture concentrations. The number of chromosome aberrations per cell was 0.0 and 0.007 in untreated and solvent control group. It was 0.027 in positive control group. The percent cells aberrated were 1.0, 0.7, 0.3 at 5 mg/ml of culture, 2.5 mg/ml of culture and 1.25 mg/ml of culture concentrations. The percent cells aberrated were 0.0 and 0.7 in untreated, solvent control group and 2.7 in the positive control group. The aberrations induced were of chromatid type only. Gaps were not considered in calculation of total aberrations in cells.

Chromosome Break Analysis

Set II (24 hours exposure)
Without metabolic activation (Table No.V)

The number of chromosome aberrations per cell was 0.01, 0.01 and 0.007 at 5 mg/ml of culture, 2.5 mg/ml of culture and 1.25 mg/ml of culture concentrations. The number of chromosome aberrations per cell was 0.0 and 0.003 in untreated and solvent control group. It was 0.030 in positive control group. The percent cells aberrated were 1.0, 1.0, 0.7 at 5 mg/ml of culture, 2.5 mg/ml of culture and 1.25 mg/ml of culture concentrations. The percent cells aberrated were 0.0 and 0.3 in untreated, solvent control group and 3.0 in the positive control group. The aberrations induced were of chromatid type only. Gaps were not considered in calculation of total aberrations in cells.

Chromosome Break Analysis

Set II (4/24 hours exposure)
With metabolic activation (Table No.VI)

The number of chromosome aberrations per cell was 0.007, 0.01 and 0.01 at 5 mg/ml of culture, 2.5 mg/ml of culture and 1.25 mg/ml of culture concentrations. The number of chromosome aberrations per cell was 0.0 and 0.003 in untreated and solvent control group. The percent cells aberrated were 0.7, 1.0, 1.0 at 5 mg/ml of culture, 2.5 mg/ml of culture and 1.25 mg/ml of culture concentrations. The percent cells aberrated were 0.0 and 0.3 in untreated, solvent control group. The aberrations induced were of chromatid type only. Gaps were not considered in calculation of total aberrations in cells.

Numerical aberrations (Appendix No.III)

Set I and Set II (4 hours exposure) and Set II (24 hours exposure):
The test item did not induce numerical aberration at any concentration, without and with metabolic activation.

REGULATORY REFERENCES

1) OECD guidelines for testing of chemicals section 4, *In vitro* Mammalian Chromosome Aberration Test, Test No.473 Adopted on 26th September 2014.

2) OECD Principles of Good Laboratory Practice: Document # 1, ENV/MC/CHEM (98)17.

3) Recommendations of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines for Laboratory Animal Facility published in The Gazette of India, December 15, 1998.

4) Requirements and Guidelines for permission to Import and/or Manufacture of New Drugs for the sale or to undertake clinical trails. Schedule "Y", Drugs and Cosmetics (IInd Amendment) Rules, Ministry of Health and Family Welfare, Government of India, January 20, 2005.

TABLE NO.I

MITOTIC INDEX OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Duration of Exposure : 4 hours

Group Number	Concentration mg per ml of culture	S9	Total Number of cells	Number of Dividing cells	Mitotic Index (%)	Reduction in Mitotic Index (%)
I	5.0	-	2000	81	4.05	0.98
		+	2002	83	4.14	2.22
II	2.5	-	2002	80	3.99	2.44
		+	2010	84	4.17	3.21
III	1.25	-	2002	82	4.09	0.00
		+	2000	80	4.00	1.23
IV	0.625	-	2004	81	4.04	1.22
		+	2005	82	4.09	0.99
V	0.312	-	2005	79	3.94	3.67
		+	2000	81	4.05	0.00
VI	10.0 µl	-	2002	82	4.09	-
		+	2000	81	4.05	-
VII	0	-	2000	80	4.00	-
		+	2004	81	4.04	-

- = Without metabolic activation
+ = With metabolic activation

TABLE NO.II

MITOTIC INDEX OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Duration of Exposure : 24 hours (-S9)
4 hours (+S9)

Group Number	Concentration mg per ml of culture	S9	Total Number of cells	Number of Dividing cells	Mitotic Index (%)	Reduction in Mitotic Index (%)
I	5.0	-	2005	82	4.09	0.00
		+	2000	82	4.10	1.00
II	2.5	-	2010	83	4.13	1.00
		+	2000	82	4.10	1.00
III	1.25	-	2004	82	4.09	0.00
		+	2001	81	4.05	-1.00
IV	0.625	-	2005	81	4.04	-1.00
		+	2010	82	4.08	1.00
V	0.312	-	2002	82	4.09	0.00
		+	2001	81	4.04	-1.00
VI	10.0 µl	-	2002	82	4.09	-
		+	2000	81	4.05	-
VII	0	-	2000	81	4.05	-
		+	2004	81	4.04	-

- = Without metabolic activation
+ = With metabolic activation

TABLE NO.III

SUMMARY OF CHROMOSOME BREAK ANALYSIS OF SET I WITHOUT METABOLIC ACTIVATION

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Duration of Exposure : 4 hours Metabolic Activation : - S9

Group Number	Treatment	Concentration mg per ml of culture	Total number of metaphases analyzed	Total No. of Aberrations	Type of aberrations			Total no. of cells with aberration	Aberration per cell	Percent Cells with Aberration
					Gap●	Chromatid	Chromosome			
I	Untreated control	0.0	300	0	0	0	0	0	0	0
II	Solvent (Negative) control	10 µl	300	1	1	1B	0	1	0.003	0.3
III	Test Item	5.0	300	3	2	3B	0	3	0.01	1.0
IV		2.5	300	3	2	3B	0	3	0.01	1.0
V		1.25	300	2	1	2B	0	2	0.007	0.7
VI	Positive ○ control	-	-	-	-	-	-	-	-	-

● = Not considered for calculations of aberrations.
○ = Positive control in this set is not included.
- S9 = Without metabolic activation

TABLE NO.IV

SUMMARY OF CHROMOSOME BREAK ANALYSIS OF SET I WITH METABOLIC ACTIVATION

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Duration of Exposure : 4 hours

Metabolic Activation : + S9

Group Number	Treatment	Concentration mg per ml of culture	Total number of metaphases analyzed	Total No. of Aberrations	Type of aberrations			Total no. of cells with aberration	Aberration per cell	Percent Cells with Aberration
					Gap●	Chromatid	Chromosome			
I	Untreated control	0.0	300	0	0	0	0	0	0	0
II	Solvent (Negative) control	10 µl	300	2	2	2B	0	2	0.007	0.7
III	Test Item	5.0	300	3	3	3B	0	3	0.01	1.0
IV		2.5	300	2	1	2B	0	2	0.007	0.7
V		1.25	300	1	0	1B	0	1	0.003	0.3
VI	Positive control	0.2 µg	300	8	4	8B	0	8	0.027	2.7*

● = Not considered for calculations of aberrations.
* = Significant at 95% level of confidence ($p \leq 0.05$)
+S9 = With metabolic activation

TABLE NO.V

SUMMARY OF CHROMOSOME BREAK ANALYSIS OF SET II WITHOUT METABOLIC ACTIVATION

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Duration of Exposure : 24 hours

Metabolic Activation : - S9

Group Number	Treatment	Concentration mg per ml of culture	Total number of metaphases analyzed	Total No. of Aberrations	Type of aberrations			Total no. of cells with aberration	Aberration per cell	Percent Cells with Aberration
					Gap●	Chromatid	Chromosome			
I	Untreated control	0.0	300	0	0	0	0	0	0	0
II	Solvent (Negative) control	10 µl	300	1	1	1B	0	1	0.003	0.3
III	Test Item	5.0	300	3	2	3B	0	3	0.01	1.0
IV		2.5	300	3	2	3B	0	3	0.01	1.0
V		1.25	300	2	1	2B	0	2	0.007	0.7
VI	Positive control	120 µg	300	9	5	9B	0	9	0.03	3.0*

● = Not considered for calculations of aberrations.
* = Significant at 95% level of confidence ($p \leq 0.05$)
- S9 = Without metabolic activation

TABLE NO.VI

SUMMARY OF CHROMOSOME BREAK ANALYSIS OF SET II WITH METABOLIC ACTIVATION

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Duration of Exposure : 4/24 hours

Metabolic Activation : + S9

Group Number	Treatment	Concentration mg per ml of culture	Total number of metaphases analyzed	Total No. of Aberrations	Type of aberrations			Total no. of cells with aberration	Aberration per cell	Percent Cells with Aberration
					Gap●	Chromatid	Chromosome			
I	Untreated control	0.0	300	0	0	0	0	0	0	0
II	Solvent (Negative) control	10 µl	300	2	0	2B	0	2	0.007	0.7
III	Test Item	5.0	300	2	1	2B	0	2	0.007	0.7
IV		2.5	300	3	0	3B	0	3	0.01	1.0
V		1.25	300	3	3	3B	0	3	0.01	1.0
VI	Positive ○ control	-	-	-	-	-	-	-	-	-

● = Not considered for calculations of aberrations.
○ = Positive control in this set is not included.
+S9 = With metabolic activation

APPENDIX NO.I

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 0.0 mg/ml of culture (Untreated Control)

Duration of Exposure : 4 hours

Metabolic activation : - S9

Culture		1			2			Total
Slide Number		1.1	1.2	◘	2.2	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	0	0	◘	0	◘	◘	0
	Chromatid Break/Fragment	0	0	◘	0	◘	◘	0
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		0	0	◘	0	◘	◘	0
Total Number of cells Aberrated		0	0	◘	0	◘	◘	0
Aberrations per cell		0	0	◘	0	◘	◘	0

◘ = Slide not scored.

- S9 = Without metabolic activation

APPENDIX NO.I (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 10 µl/ml of culture Solvent Control (Negative Control)

Duration of Exposure : 4 hours Metabolic activation : - S9

Culture		5			6			Total
Slide Number		5.1	5.2	◘	6.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	1	0	◘	0	◘	◘	1
	Chromatid Break/Fragment	1B	0	◘	0	◘	◘	1B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		1	0	◘	0	◘	◘	1
Total Number of cells Aberrated		1	0	◘	0	◘	◘	1
Aberrations per cell		0.01	0	◘	0	◘	◘	0.003

◘ = Slide not scored.
- S9 = Without metabolic activation

APPENDIX NO.I (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 1.25 mg/ml of culture

Duration of Exposure : 4 hours

Metabolic activation : - S9

Culture		13			14			Total
Slide Number		13.1	◘	◘	14.2	14.3	◘	3
Total Number of Metaphases Analyzed		100	◘	◘	100	100	◘	300
Type of Aberrations	Gap	0	◘	◘	1	0	◘	1
	Chromatid Break/Fragment	1B	◘	◘	1B	0	◘	2B
	Chromosome	0	◘	◘	0	0	◘	0
Total Number of Aberrations		1	◘	◘	1	0	◘	2
Total Number of cells Aberrated		1	◘	◘	1	0	◘	2
Aberrations per cell		0.01	◘	◘	0.01	0	◘	0.007

◘ = Slide not scored.
- S9 = Without metabolic activation

APPENDIX NO.I (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 2.5 mg/ml of culture

Duration of Exposure : 4 hours

Metabolic activation : - S9

Culture		17			18			Total
Slide Number		17.1	◘	◘	18.1	18.2	◘	3
Total Number of Metaphases Analyzed		100	◘	◘	100	100	◘	300
Type of Aberrations	Gap	0	◘	◘	1	1	◘	2
	Chromatid Break/Fragment	1B	◘	◘	1B	1B	◘	3B
	Chromosome	0	◘	◘	0	0	◘	0
Total Number of Aberrations		1	◘	◘	1	1	◘	3
Total Number of cells Aberrated		1	◘	◘	1	1	◘	3
Aberrations per cell		0.01	◘	◘	0.01	0.01	◘	0.01

◘ = Slide not scored.
B = Break
- S9 = Without metabolic activation

APPENDIX NO.I (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 5.0 mg/ml of culture

Duration of Exposure : 4 hours

Metabolic activation : - S9

Culture		21		◘	22	◘	◘	Total
Slide Number		21.1	21.2	◘	22.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	1	1	◘	0	◘	◘	2
	Chromatid Break/Fragment	2B	1B	◘	0	◘	◘	3B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		2	1	◘	0	◘	◘	3
Total Number of cells Aberrated		2	1	◘	0	◘	◘	3
Aberrations per cell		0.02	0.01	◘	0	◘	◘	0.01

◘ = Slide not scored.
- S9 = Without metabolic activation

APPENDIX NO.I (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 0.0 mg/ml of culture (Untreated control)

Duration of Exposure : 4 hours Metabolic activation : + S9

Culture		3			4			Total
Slide Number		3.1	3.2	◘	4.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	0	0	◘	0	◘	◘	0
	Chromatid Break/Fragment	0	0	◘	0	◘	◘	0
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		0	0	◘	0	◘	◘	0
Total Number of cells Aberrated		0	0	◘	0	◘	◘	0
Aberrations per cell		0	0	◘	0	◘	◘	0

◘ = Slide not scored.
+S9 = With metabolic activation

APPENDIX NO.I (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 10 µl/ml of culture Solvent Control (Negative Control)

Duration of Exposure : 4 hours Metabolic activation : + S9

Culture		7		◘	8	◘	◘	Total
Slide Number		7.1	7.2	◘	8.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	1	1	◘	0	◘	◘	2
	Chromatid Break/Fragment	1B	1B	◘	0	◘	◘	2B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		1	1	◘	0	◘	◘	2
Total Number of cells Aberrated		1	1	◘	0	◘	◘	2
Aberrations per cell		0.01	0.01	◘	0	◘	◘	0.007

◘ = Slide not scored.
+S9 = With metabolic activation

APPENDIX NO.I (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 0.2 µg/ml of Culture (Benzo[a] pyrene)

Duration of Exposure : 4 hours Metabolic activation : + S9

Culture		9			10			Total
Slide Number		9.1	9.2	◘	10.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	2	1	◘	1	◘	◘	4
	Chromatid Break/Fragment	3B	2B	◘	3B	◘	◘	8B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		3	2	◘	3	◘	◘	8
Total Number of cells Aberrated		3	2	◘	3	◘	◘	8
Aberrations per cell		0.03	0.02	◘	0.03	◘	◘	0.027

◘ = Slide not scored.
B =Break
+S9 = With metabolic activation

APPENDIX NO.I (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 1.25 mg/ml of culture

Duration of Exposure : 4 hours

Metabolic activation : + S9

Culture		15			16			Total
Slide Number		15.1	◘	◘	16.1	16.2	◘	3
Total Number of Metaphases Analyzed		100	◘	◘	100	100	◘	300
Type Of Aberrations	Gap	0	◘	◘	0	0	◘	0
	Chromatid Break/Fragment	1B	◘	◘	0	0	◘	1B
	Chromosome	0	◘	◘	0	0	◘	0
Total Number of Aberrations		1	◘	◘	0	0	◘	1
Total Number of cells Aberrated		1	◘	◘	0	0	◘	1
Aberrations per cell		0.01	◘	◘	0	0	◘	0.003

◘ = Slide not scored.
+S9 = With metabolic activation

APPENDIX NO.I (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 2.5 mg/ml of culture

Duration of Exposure : 4 hours

Metabolic activation : + S9

Culture		19			20			Total
Slide Number		19.1	◘	◘	20.1	20.3	◘	3
Total Number of Metaphases Analyzed		100	◘	◘	100	100	◘	300
Type of Aberrations	Gap	0	◘	◘	0	1	◘	1
	Chromatid Break/Fragment	1B	◘	◘	0	1B	◘	2B
	Chromosome	0	◘	◘	0	0	◘	0
Total Number of Aberrations		1	◘	◘	0	1	◘	2
Total Number of cells Aberrated		1	◘	◘	0	1	◘	2
Aberrations per cell		0.01	◘	◘	0	0.01	◘	0.007

◘ = Slide not scored.
B = Break
+S9 = With metabolic activation

APPENDIX NO.I (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 5.0 mg/ml of culture

Duration of Exposure : 4 hours Metabolic activation : + S9

Culture		23			24			Total
Slide Number		23.1	23.3	◘	24.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	1	1	◘	1	◘	◘	3
	Chromatid Break/Fragment	1B	1B	◘	1B	◘	◘	3B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		1	1	◘	1	◘	◘	3
Total Number of cells Aberrated		1	1	◘	1	◘	◘	3
Aberrations per cell		0.01	0.01	◘	0.01	◘	◘	0.01

◘ = Slide not scored.
+S9 = With metabolic activation

APPENDIX NO.II

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 1.25 mg/ml of culture

Duration of Exposure : 24 hours

Metabolic activation : - S9

Culture		25			26			Total
Slide Number		25.1	25.2	◘	26.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	1	0	◘	0	◘	◘	1
	Chromatid Break/Fragment	1B	0	◘	1B	◘	◘	2B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		1	0	◘	1	◘	◘	2
Total Number of cells Aberrated		1	0	◘	1	◘	◘	2
Aberrations per cell		0.01	0	◘	0.01	◘	◘	0.007

◘ = Slide not scored.
B = Break
- S9 = Without metabolic activation

APPENDIX NO.II (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 2.5 mg/ml of culture

Duration of Exposure : 24 hours

Metabolic activation : - S9

Culture		29			30			Total
Slide Number		29.1	29.2	◘	30.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	0	1	◘	1	◘	◘	2
	Chromatid Break/Fragment	1B	1B	◘	1B	◘	◘	3B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		1	1	◘	1	◘	◘	3
Total Number of cells Aberrated		1	1	◘	1	◘	◘	3
Aberrations per cell		0.01	0.01	◘	0.01	◘	◘	0.03

◘ = Slide not scored.
B = Break
- S9 = Without metabolic activation

APPENDIX NO.II (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 5.0 mg/ml of culture

Duration of Exposure : 24 hours

Metabolic activation : - S9

Culture		33			34			Total
Slide Number		33.1	33.2	◘	34.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	1	0	◘	1	◘	◘	2
	Chromatid Break/Fragment	1B	1B	◘	1B	◘	◘	3B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		1	1	◘	1	◘	◘	3
Total Number of cells Aberrated		1	1	◘	1	◘	◘	3
Aberrations per cell		0.01	0.01	◘	0.01	◘	◘	0.01

◘ = Slide not scored.
B = Break
- S9 = Without metabolic activation

APPENDIX NO.II (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 0.0 mg/ml of culture (Untreated Control)

Duration of Exposure : 24 hours

Metabolic activation : - S9

Culture		37			38			Total
Slide Number		37.1	37.2	◘	38.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	0	0	◘	0	◘	◘	0
	Chromatid Break/Fragment	0	0	◘	0	◘	◘	0
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		0	0	◘	0	◘	◘	0
Total Number of cells Aberrated		0	0	◘	0	◘	◘	0
Aberrations per cell		0	0	◘	0	◘	◘	0

◘ = Slide not scored.
- S9 = Without metabolic activation

APPENDIX NO.II (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 10 µl/ml of culture Solvent Control (Negative Control)

Duration of Exposure : 24 hours Metabolic activation : - S9

Culture		41		◘	42	◘	◘	Total
Slide Number		41.1	41.2	◘	42.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	1	0	◘	0	◘	◘	1
	Chromatid Break/Fragment	1B	0	◘	0	◘	◘	1B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		1	0	◘	0	◘	◘	1
Total Number of cells Aberrated		1	0	◘	0	◘	◘	1
Aberrations per cell		0.01	0	◘	0	◘	◘	0.003

◘ = Slide not scored.
- S9 = Without metabolic activation

APPENDIX NO.II (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 120 µg/ml of Culture (Ethyl Methane Sulphonate)

Duration of Exposure : 24 hours Metabolic activation : - S9

Culture		11			12			Total
Slide Number		11.1	11.2	◘	12.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	2	2	◘	1	◘	◘	5
	Chromatid Break/Fragment	3B	3B	◘	3B	◘	◘	9B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		3	3	◘	3	◘	◘	9
Total Number of cells Aberrated		3	3	◘	3	◘	◘	9
Aberrations per cell		0.03	0.03	◘	0.03	◘	◘	0.03

◘ = Slide not scored.
B = Break
- S9 = Without metabolic activation

APPENDIX NO.II (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 1.25 mg/ml of culture

Duration of Exposure : 4/24 hours

Metabolic activation : + S9

Culture		27		◘	28	◘	◘	Total
Slide Number		27.1	27.2	◘	28.2	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	2	1	◘	0	◘	◘	3
	Chromatid Break/Fragment	2B	1B	◘	0	◘	◘	3B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		2	1	◘	0	◘	◘	3
Total Number of cells Aberrated		2	1	◘	0	◘	◘	3
Aberrations per cell		0.02	0.01	◘	0	◘	◘	0.01

◘ = Slide not scored.
+S9 = With metabolic activation

APPENDIX NO.II (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 2.5 mg/ml of culture

Duration of Exposure : 4/24 hours

Metabolic activation : + S9

Culture		31			32			Total
Slide Number		31.1	31.2	◘	32.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	0	1	◘	0	◘	◘	1
	Chromatid Break/Fragment	1B	1B	◘	1B	◘	◘	3B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		1	1	◘	1	◘	◘	3
Total Number of cells Aberrated		1	1	◘	1	◘	◘	3
Aberrations per cell		0.01	0.01	◘	0.01	◘	◘	0.01

◘ = Slide not scored.
+S9 = With metabolic activation

APPENDIX NO.II (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 5.0 mg/ml of culture

Duration of Exposure : 4/24 hours

Metabolic activation : + S9

Culture		35		◘	36	◘	◘	Total
Slide Number		35.1	35.2	◘	36.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	0	1	◘	0	◘	◘	1
	Chromatid Break/Fragment	1B	1B	◘	0	◘	◘	2B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		1	1	◘	0	◘	◘	2
Total Number of cells Aberrated		1	1	◘	0	◘	◘	2
Aberrations per cell		0.01	0.01	◘	0	◘	◘	0.007

◘ = Slide not scored.
B = Break
+S9 = With metabolic activation

APPENDIX NO.II (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 0.0 mg/ml of culture (Untreated Control)

Duration of Exposure : 4/24 hours Metabolic activation : + S9

Culture		39			40			Total
Slide Number		39.1	39.2	◘	40.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	0	0	◘	0	◘	◘	0
	Chromatid Break/Fragment	0	0	◘	0	◘	◘	0
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		0	0	◘	0	◘	◘	0
Total Number of cells Aberrated		0	0	◘	0	◘	◘	0
Aberrations per cell		0	0	◘	0	◘	◘	0

◘ = Slide not scored.
+S9 = With metabolic activation

APPENDIX NO.II (Contd.)

CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Conc. : 10 µl/ml of culture Solvent Control (Negative Control)

Duration of Exposure : 4/24 hours Metabolic activation : + S9

Culture		43		◘	44	◘	◘	Total
Slide Number		43.1	43.2	◘	44.1	◘	◘	3
Total Number of Metaphases Analyzed		100	100	◘	100	◘	◘	300
Type of Aberrations	Gap	0	1	◘	0	◘	◘	1
	Chromatid Break/Fragment	1B	1B	◘	0	◘	◘	2B
	Chromosome	0	0	◘	0	◘	◘	0
Total Number of Aberrations		1	1	◘	0	◘	◘	2
Total Number of cells Aberrated		1	1	◘	0	◘	◘	2
Aberrations per cell		0.01	0.01	◘	0	◘	◘	0.007

◘ = Slide not scored.
+S9 = With metabolic activation

APPENDIX NO.III

NUMERICAL ABERRATIONS IN HUMAN LYMPHOCYTES *IN VITRO* OF SET I AND SET II

Laboratory Test Item Code : TAS/002/015
Test System : Human Lymphocyte Culture

Group Number	Concentration mg/ml of culture	S9	Duration of Exposure (hours)			
			4 P	4 E	4 / 24 P	4 / 24 E
I	Untreated Control	-	0	0	0	0
		+	0	0	0	0
II	Solvent (Negative) Control	-	0	0	0	0
		+	0	0	0	0
III	5.0	-	0	0	0	0
		+	0	0	0	0
IV	2.5	-	0	0	0	0
		+	0	0	0	0
V	1.25	-	0	0	0	0
		+	0	0	0	0

- = Without metabolic activation
+ = With metabolic activation
P : Polyploidy
E : Endoreduplication

APPENDIX NO.IV

HISTORICAL DATA OF *IN VITRO* MAMMALIAN CHROMOSOME ABERRATION TEST

Test System : Human Lymphocytes

Duration of Exposure : 4 hours

Metabolic Activation : - S9

Parameter: Percent Cells with Aberration

Study Number	Untreated Control	Positive Control	Vehicle/Solvent (Negative Control)			Historical Data Made On
			Distilled Water	DMSO	DMF	
	Mean	Mean	Mean	Mean	Mean	
Average	0.00	-	0.13	0.22	1.00	31-10-2013
17431	0.0	-	0.0	-	-	27-02-2014
17436	0.0	-	0.5	-	-	04-04-2014
Average	0.00	-	0.21	0.22	1.00	

APPENDIX NO.IV (Contd.)

HISTORICAL DATA OF *IN VITRO* MAMMALIAN CHROMOSOME ABERRATION TEST

Test System : Human Lymphocytes

Duration of Exposure : 4 hours

Metabolic Activation : + S9

Parameter: Percent Cells with Aberration

Study Number	Untreated Control	Positive Control	Vehicle/Solvent (Negative Control)			Historical Data Made On
			Distilled Water	DMSO	DMF	
	Mean	Mean	Mean	Mean	Mean	
Average	0.00	4.30	0.07	0.24	1.00	31-10-2013
17431	0.0	3.0	0.0	-	-	27-02-2014
17436	0.0	3.5	0.5	-	-	04-04-2014
Average	0.00	3.60	0.19	0.24	1.00	

APPENDIX NO.IV (Contd.)

HISTORICAL DATA OF *IN VITRO* MAMMALIAN CHROMOSOME ABERRATION TEST

Test System : Human Lymphocytes

Duration of Exposure : 24 hours

Metabolic Activation : - S9

Parameter: Percent Cells with Aberration

Study Number	Untreated Control	Positive Control	Vehicle/Solvent (Negative Control)			Historical Data Made On
			Distilled Water	DMSO	DMF	
	Mean	Mean	Mean	Mean	Mean	
Average	0.13	4.66	0.13	0.32	1.00	31-10-2013
17431	0.0	3.0	0.0	-	-	27-02-2014
17436	0.0	3.5	0.5	-	-	04-04-2014
Average	0.04	3.72	0.21	0.32	1.00	

APPENDIX NO.IV (Contd.)

HISTORICAL DATA OF *IN VITRO* MAMMALIAN CHROMOSOME ABERRATION TEST

Test System : Human Lymphocytes

Duration of Exposure : 4 hours

Metabolic Activation : + S9

Parameter: Percent Cells with Aberration

Study Number	Untreated Control	Positive Control	Vehicle/Solvent (Negative Control)			Historical Data Made On
			Distilled Water	DMSO	DMF	
	Mean	Mean	Mean	Mean	Mean	
Average	0.01	-	0.13	0.28	1.00	31-10-2013
17431	0.0	-	0.0	-	-	27-02-2014
17436	0.0	-	0.5	-	-	04-04-2014
Average	0.003	-	0.21	0.28	1.00	

ANNEXURE - I

Certificate of Analysis (1 Page)

ANNEXURE - II

Certificate of Approval
(Good Laboratory Practice, GLP)
(1 Page)

ANNEXURE - III

Summary of Amendment(s) to the Study Plan (1 Page)

Summary of Amendment(s) to the Study Plan

Amendment Number	Amendment
1	1.1) The Study Schedule dates finalized. 1.2) OECD guideline number 473 revised, hence study plan requires amendment for scoring of metaphases as per the new revised guideline.
2	2.1) Experimental Completion Date added and Study Completion Date finalized

INDIAN INSTITUTE OF TOXICOLOGY

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FINAL REPORT

IIT STUDY NUMBER 17956

REPEATED DOSE 90-DAY ORAL TOXICITY STUDY WITH RHIZOPUS LIPASE BY DAILY GAVAGE IN THE RAT FOLLOWED BY A 4 WEEK RECOVERY PERIOD

STUDY DIRECTOR
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REGULATORY REQUIREMENTS:

OECD Guideline for the testing of Chemicals No. 408, "Repeated Dose-90 day Oral Toxicity Study in Rodents" adopted on 21st September, 1998.

CONFIDENTIAL

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STATEMENT OF GLP COMPLIANCE

Title of the Study	: Repeated Dose 90-day Oral Toxicity Study with Rhizopus Lipase by daily gavage in the Rat followed by a 4 week recovery period.
Study Number	: 17956
Study Plan Number	: SPL/002/058
Name of the Test item	: Rhizopus Lipase

The study was conducted in accordance with the Good Laboratory Practice Principles as Published by the OECD in 1998, No 1 ENV/MC/CHEM(98)17.

Mr. V.M.Bhide M.B.A.	(b) (6)	27·01·2015
Test Facility Management	Signature	Date

STATEMENT OF COMPLIANCE WITH GOOD LABORATORY PRACTICE

Title of the Study	: Repeated Dose 90-day Oral Toxicity Study with Rhizopus Lipase by daily gavage in the Rat followed by a 4 week recovery period.
Study Number	: 17956
Study Plan Number	: SPL/002/058
Name of the Test item	: Rhizopus Lipase

The study was conducted in compliance to the Good Laboratory Principles as Published by OECD in 1998, No 1 ENV/MC/CHEM(98)17.

The study was conducted in compliance to the written Study Plan approved by the Study Director and authorized by the Sponsor and Indian Institute of Toxicology Management and all applicable Standard Operating Procedures of Indian Institute of Toxicology, Pune.

All original Raw Data including documentation, signed Study Plan, Study Plan Amendments, reserve sample, a copy of Final Report and specimen (wet tissue bottles, wax block, histopathology slides and smears for differential WBC count) are archived at Indian Institute of Toxicology, Pune.

I accept responsibility for the conduct of the study and hereby declare that the study was conducted under my direction. This report is a complete, true and accurate record of the results obtained.

The sponsor is responsible for Good laboratory Practice (GLP) compliance for all Test Item information and test item prepared formulation analyses and its report provided to the Indian Institute of Toxicology, Pune.

Dr. R.M.Bhide Ph.D., ERT	(b) (6)	27/1/2015
Study Director	Signature	Date

STATEMENT OF QUALITY ASSURANCE UNIT

Title of the Study : Repeated Dose 90-day Oral Toxicity Study with Rhizopus Lipase by daily gavage in the Rat followed by a 4 week recovery period.

Study Number : 17956

Study Plan Number : SPL/002/058

Name of the Test item : Rhizopus Lipase

This study has been audited and the final report has been examined with respect to study plan, SOP and raw data. The report is true reflection of the raw data and the study was conducted in compliance with the principles of GLP. The audits were carried out according to the applicable SOP's of Quality Assurance Unit of Indian Institute of Toxicology, Pune. These reports are kept in the archives at Indian Institute of Toxicology, Pune.

Inspections were made by the Quality Assurance Unit of the Indian Institute of Toxicology for different phases of the study described in this report. The dates on which the inspections were made and the dates on which the findings were reported to the Study Director and to the facility Management are given below.

Date(s) of Inspection	Phases Inspected	Date(s) findings reported to Study Director	Date(s) findings reported to Management
09-07-2014	Study Plan Review	09-07-2014	09-07-2014
29-07-2013	Pre-study Verification	29-07-2013	29-07-2013
29-07-2013	Amendment - 1	29-07-2013	29-07-2013
04-08-2014	Randomization of Study Animals	04-08-2014	04-08-2014
05-08-2014	Randomization of Study Animals	05-08-2014	05-08-2014
05-08-2014	Test Item Preparation	05-08-2014	05-08-2014
05-08-2014	Handling, Sampling, Labeling and Transport of Test Item for Analysis	05-08-2014	05-08-2014
06-08-2014	Test Item Preparation	06-08-2014	06-08-2014
06-08-2014	Test Item Administration - Gavage	06-08-2014	06-08-2014
14-08-2014	Clinical Signs Observation	14-08-2014	14-08-2014
19-08-2014	Body Weight, Feed Consumption	19-08-2014	19-08-2014
05-09-2014	Safety / Environmental Monitoring	05-09-2014	05-09-2014
23-09-2014	Handling, Sampling, Labeling and Transport of Test Item for Analysis	23-09-2014	23-09-2014
26-09-2014	Handling, Weighing of Test Item	26-09-2014	26-09-2014
27-09-2014	Raw Data Audit (Interim)	27-09-2014	27-09-2014
28-10-2014	Handling, Sampling, Labeling and Transport of Test Item for Analysis	28-10-2014	28-10-2014
01-11-2014	Urine Analyses	01-11-2014	01-11-2014
03-11-2014	Necropsy, Haematology	03-11-2014	03-11-2014
04-11-2014	Necropsy, Clinical Chemistry	04-11-2014	04-11-2014
01-12-2014	Haematology	01-12-2014	01-12-2014
02-12-2014	Clinical Chemistry	02-12-2014	02-12-2014
09-12-2014	Histopathology Technique: Processing	09-12-2014	09-12-2014
15-01-2015 to 16-01-2015	Raw Data Audit	16-01-2015	16-01-2015
17-01-2015 to 19-01-2015	Report Table Audit	19-01-2015	19-01-2015
19-01-2015	Draft Report Audit	19-01-2015	19-01-2015
23-01-2015	Amendment - 2	23-01-2015	23-01-2015
27-01-2015	Final Report Audit	27-01-2015	27-01-2015

Dr. P.R.Tikhe Ph.D. (b) (6) 27.01.2015

Quality Assurance Unit Signature Date

LIST OF ABBREVIATIONS

IIT	-	Indian Institute of Toxicology
GLP	-	Good Laboratory Practice
OECD	-	Organization for Economic Co-operation and Development
SOP	-	Standard Operating Procedure
G	-	Gram
mg	-	Milligram
mcg	-	Microgram
mg%	-	Milligram Percent
Kg	-	Kilogram
°C	-	Degree Celsius
%	-	Percent
No.	-	Number
Nos.	-	Numbers
ml	-	Milliliter
mm	-	Millimeter
e.g.	-	For Example
Ltd.	-	Limited
Contd.	-	Continued
TS	-	Terminal sacrifice
NAD	-	No abnormality detected
min.	-	Minutes
hrs.	-	Hours
Rev.	-	Reversal
EDTA	-	Ethylene Di-amine Tetra Acetic Acid
d/L	-	Deciliter
f/L	-	Fentoliter
µl	-	Micro liter
r.p.m.	-	Revolution Per Minute
CO_2	-	Carbon Dioxide
i.e.	-	That is
IU/L	-	International Unit per Liter
U/L	-	Unit per Liter
mmol/l	-	Milimole per liter
pg	-	Pico gram
μm^3	-	Cubic micro meter
Hb	-	Haemoglobin
RBC	-	Red Blood Corpuscles
HCT	-	Haematocrit
MCV	-	Mean Corpuscular Volume
MCH	-	Mean Corpuscular Haemoglobin
MCHC	-	Mean Corpuscular Haemoglobin Concentration

LIST OF ABBREVIATIONS (Contd.)

WBC	-	White Blood Corpuscles
N	-	Neutrophils
L	-	Lymphocytes
E	-	Eosinophils
M	-	Monocytes
B	-	Basophils
Pt.	-	Prothrombin time
ALT	-	Alanine Aminotransferase
AST	-	Aspartate Aminotransferase
ALP	-	Alkaline Phosphatase
Sec.	-	Second

STUDY SCHEDULE

Study Schedule:

Study Initiation Date	:	09-07-2014	
Experimental Starting Date	:	04-08-2014	
		Male	Female
Day of First Dosing	:	05-08-2014	06-08-2014
Day of Last Dosing	:	02-11-2014	03-11-2014
Day of Necropsy (91st day)	:	03-11-2014	04-11-2014
Day of Necropsy (119th day)	:	01-12-2014	02-12-2014
Experimental Completion Date	:	16-01-2015	
Study Completion Date	:	27-01-2015	
Date of Reporting	:	27-01-2015	

PERSONNEL INVOLVED IN THE STUDY

Study Director	: Dr. R.M.Bhide Ph.D., ERT
Alternate Study Director	: Dr. R.P.Dighe Ph.D.
Veterinarian	: Dr. S.N.Khutale M.V.Sc.
Study Scientists	: Mr. M.P.Pawar B.Sc. Mr. D.D.Gawande M.Pharm. Miss S.V.Patil M.Sc. Mr. M.P.Supekar M.Pharm. Mr. J.M.Sonpetkar M.Pharm.
Pathology	: Dr. V.V.Dange M.V.Sc. Dr. S.S.Kad M.V.Sc.
Clinical Pathology	: Miss S.K.Pise M.Sc.
Necropsy	: Dr. V.V.Dange M.V.Sc. Dr. S.N.Khutale M.V.Sc. Dr. S.S.Kad M.V.Sc. Mr. M.P.Pawar B.Sc. Miss S.V.Patil M.Sc. Dr. P.U.Kore M.V.Sc. Mr. D.D.Gawande M.Pharm. Mr. M.P.Supekar M.Pharm. Mr. J.M.Sonpetkar M.Pharm.
Histology Techniques	: Dr. V.V.Dange M.V.Sc. Miss S.K.Pise M.Sc. Miss D.B.Survase M.Sc. Dr. P.U.Kore M.V.Sc. Mr. G.R.Palve
Statistics	: Mr. S.D.Nagpure B.Com. Mr. D.K.Raut H.S.C.
Quality Assurance Unit	: Dr. P.R.Tikhe Ph.D. Dr. R.M.Gosavi M.V.Sc.
Report Preparation	: Dr. R.M.Bhide Ph.D., ERT Mr. S.D.Nagpure B.Com.

SUMMARY AND CONCLUSION

The Repeated Dose 90-day Oral Toxicity study followed by a 4 week recovery period was designed and conducted to determine the toxicity profile of **Rhizopus Lipase** when administered daily for 90 days in the Sprague Dawley rats.

Rhizopus Lipase was administered to animals at the dose levels of 250 mg/kg, 500 mg/kg and 1000 mg/kg body weight. Two additional dose levels were added to the study as 0 mg/kg (Rev.) and 1000 mg/kg (Rev.), in order to study the reversibility or delayed occurrence of symptoms, if any. The control animals were administered with vehicle (distilled water) only. The doses were selected based on the results of the Acute Toxicity Study and Dose Range Finder Study conducted at Indian Institute of Toxicology, Pune.

Salient features of the study were as follows:

1) All the male and female animals from control and different dose groups up to 1000 mg/kg survived throughout the dosing period of 90 days and the recovery period of 28 days.

2) Male and female animals from control and different dose groups exhibited normal body weight gain at the end of the dosing period of 90 days and the recovery period of 28 days.

3) Feed intake of animals from control and different dose groups was found to be comparable throughout the dosing period of 90 days and the recovery period of 28 days.

4) Ophthalmoscopic examination, conducted prior to and at the end of dosing period on animals from control and different dose groups did not reveal any abnormality.

5) No signs of toxicity were observed in male and female animals from different dose groups during the dosing period of 90 days and the recovery period of 28 days.

6) Detailed clinical observations conducted at weekly interval (upto 17^{th} week) did not reveal any abnormality in all male and female animals from control and different dose groups during the dosing period of 90 days and the recovery period of 28 days.

7) Towards the end of the exposure period in week 13, functional observation battery such as sensory reactivity to stimuli of different types (e.g. auditory, visual and proprioceptive stimuli) revealed no abnormalities attributable to the treatment.

Grip strength values observed in male and female animals for control and different dose groups were comparable.

Motor activity values observed in male and female animals for control and different dose groups were comparable.

8) Haematological analysis in male and female animals conducted at the end of the dosing period on day 91, revealed statistically significant increase in the values of Hb, HCT and Total WBC (500 mg/kg, male), MCV (250 mg/kg, female), Total WBC (500 mg/kg, female), statistically significant decrease in the values of Hb and MCH (250 mg/kg, male) and Platelets (1000 mg/kg, female).

Haematological analysis in male and female animals conducted at the end of the recovery period on day 119, revealed statistically significant increase in the values of Lymphocytes (1000 mg/kg, male and female) and statistically significant decrease in the values of Neutrophils (1000 mg/kg, male and female).

The increase/decrease in the values of various parameters was marginal and within the normal biological and laboratory limits.

9) Clinical biochemistry analysis in male and female animals conducted at the end of the dosing period on day 91, revealed statistically significant increase in the values of Creatinine (500 mg/kg, male), Total Protein, Globulin and Cholesterol (500 mg/kg, female), Aspartate Aminotransferase (500 mg/kg and 1000 mg/kg, female) and Creatinine (1000 mg/kg, female). In addition statistically significant decrease was observed in the values of Total Protein and Glucose (1000 mg/kg, male), Alanine Aminotransferase (250 mg/kg, 500 mg/kg and 1000 mg/kg, male), Alkaline Phosphatase (250 mg/kg female), Glucose (1000 mg/kg female), Bilirubin (250 mg/kg and 1000 mg/kg, female) and Chloride (500 mg/kg and 1000 mg/kg, female).

At the end of the recovery period on day 119 (Reversal groups) statistically significant increase was observed in the values of Potassium (1000 mg/kg, male), Globulin (1000 mg/kg, female) and statistically significant decrease was observed in the values of Chloride (1000 mg/kg, male).

The increase/decrease in the values of various parameters was marginal and within the normal biological and laboratory limits.

10) Urine analysis conducted during 13th and 17th week of dosing period (on day 86, 87, 88 and 119), revealed no abnormality attributable to the treatment. Slightly higher volume of urine analysis was observed in female animals from 1000 mg/kg dose group.

11) At termination of dosing on day 91, male animals from 500 mg/kg and 1000 mg/kg dose groups revealed decreased relative weights of epididymides when compared with that of controls.

Organ weight data of male animals sacrificed on day 119 from 1000 mg/kg reversal group, was found to be comparable with that of controls.

At termination of dosing on day 91, female animals from 500 mg/kg dose group revealed increased relative weights of adrenals and decreased relative weights of ovaries was observed in animals from 250 mg/kg dose group when compared with that of controls.

Organ weight data of female animals sacrificed on day 119 from 1000 mg/kg reversal group, revealed increased relative weights of spleen when compared with that of controls.

Although significant changes in the values of organ weight was observed in male and female animals from different dose groups, no related gross pathological and histopathological findings were seen, hence these findings were considered to be of no toxicological importance.

12) Gross pathological examination did not reveal any abnormality attributable to the treatment.

13) Histopathological examination did not reveal any abnormality attributable to the treatment.

Based on these findings the No Observed Adverse Effect Level (NOAEL) of **Rhizopus Lipase** supplied by **Advanced Enzyme Technologies Ltd., Thane,** in the Sprague Dawley rat via oral route, over a period of 90 days was found to be 1000 mg/kg body weight in male and female animals.

(b) (6)

DR. R.M.BHIDE Ph.D., ERT
STUDY DIRECTOR

1) The results relate only to the items tested.
2) This report shall not be reproduced except in full, without the written approval of the laboratory.

Purpose

The purpose of this study was to assess toxicological profile of **Rhizopus Lipase**, to determine target organ of toxicity, its reversibility and No Observed Adverse Effect Level (NOAEL) in the rat after 90 consecutive days of oral administration.

MATERIALS AND METHODS

TEST ITEM

Sponsor	: **Advanced Enzyme Technologies Ltd., Thane**
Laboratory Sponsor Code	: **SPN/002**
Test Item	: **Rhizopus Lipase**
Batch Number	: **011423**
Laboratory Test Item Code	: **TAS/002/015**
Manufacturing Date	: **January, 2014**
Expiry Date	: **December, 2015**
Consistency	: **Solid powder**
Activity (Clinical Indication)	: **Food Enzyme**
Personnel Safety Data	: Safety precautions included use of protective clothing, gloves, mask and eye protection glasses.
Test Item Analysis	: Determination and documentation of the identity, strength, purity, stability and uniformity of the test item as defined in the Good Laboratory Practice (GLP) regulations, is the responsibility of the Sponsor. The Sponsor provided these test item characterization data (A Certificate of Analysis) for review by the Study Director and inclusion in the final report.
Test Item prepared solution(s) analysis (Main Study)	: Concentration and stability analyses was conducted for test item prepared solution(s) on day 1 (05-08-2014), in week 7 (23-09-2014) and in week 13 (28-10-2014) of the study.
Test Item prepared solution(s) storage	: For the period till the delivery to Sponsor the test item solution(s) were stored at ambient temperature. The solution were shipped to Sponsor in a thermocol box during the transport at the following address: Advanced Enzyme Technologies Ltd., Sun Magnetica, 'A' wing, 5th Floor, LIC Service Road, Louiswadi, Thane (W) 400 604, Maharashtra, India.
Stability Data	: Information on file with the Sponsor.
Storage Requirements	: Test Item and Test Item Prepared solutions were stored at ambient temperature.
Preparation of Test Item (Main Study)	: The test item was dissolved in distilled water to obtain 25 mg/ml, 50 mg/ml and 100 mg/ml strength of formulations.
Vehicle	: Distilled water

Disclaimer :

The above physiochemical data of test substance is supplied by the Sponsor. All responsibility with regards to the accuracy and authenticity of this information remains with the Sponsor. The test lab is not responsible for any variations with the batch number supplied.

Test System

Species: Rat

Strain: Sprague Dawley.

Sex: Male and females equal numbers, females were nulliparous and non-pregnant.

Number of Animals:
Main Study animals: 104 (52 males and 52 females)

Source: National Institute of Biosciences, Pune a registered source as approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Justification for selection of the rat as the test system:

1) In order to meet the regulatory requirement for testing in a rodent species;
2) Widely used in as a species of choice for pre-clinical toxicological studies.
3) This strain is widely used throughout the industry in the non-clinical laboratory studies.
4) This study is intended to provide information on the health hazards likely to arise from exposure to the test item.

Selection of Animals:

The health examination was performed by a study veterinarian. No abnormal findings were noted in clinical chemistry, haematology and gross pathological examination in animals studied to assess the health status; hence the lot received was quarantined for a period of 7 days. The general health of the animals was reviewed throughout the quarantine period. The animals were transferred to study room for acclimatization to laboratory conditions for minimum of 5 days prior to dosing.
The animals of uniform body weight were selected. The individual body weights of the animals did not exceed ± 20% of group mean body weight. The group means body weights of all the groups were approximately equal.

Body Weight and Age:

The animals were 5 to 7 weeks old at the time of assignment to the study.
Body weights at the start (day 0) :

Male	Mean	: 125.84 g (= 100 %)
	Minimum	: 111.5 g (- 11.40 %)
	Maximum	: 144.2 g (+ 14.59 %)
	Total No. of animals	: 52
Female	Mean	: 118.53 g (= 100 %)
	Minimum	: 102.1 g (- 13.86 %)
	Maximum	: 129.7 g (+ 9.42 %)
	Total No. of animals	: 52

Identification:

Each animal was individually identified by the pieric acid marking. A group of animals in one cage was additionally identified by the label affixed to each cage. A label according to groups identified the cage and each label contained information on cage and study number. It also bear species, strain, sex and identification numbers of rats within it.

Grouping, Randomization and Management:

A total of 104 animals (52 males + 52 females) were selected and randomly distributed into six groups with 10 animals/sex/group for main groups and 6 animals /sex /group for reversal group.

At the commencement of the study the weight variation of animals used were minimal and did not exceed ± 20 % of the mean weight of each sex.

Environmental Conditions

Housing:

The rats were housed in polycarbonate cages with paddy as bedding.
After allocation to respective dose groups rats were housed 2/sex/cage.

Room Air, Temperature and Humidity:

The animal room was independently provided with at least ten air changes per hour of 100% fresh air that has been passed through the HEPA filters. Room temperature was maintained at 22 ± 3°C (actual range, 19.2 °C to 22.6 °C) and room humidity was maintained at 30% to 70% (actual range, 53.1% to 60.1%).

Light:

An artificial light and dark cycle of 12 hours each was provided to the room.

Diet:

Rodent feed supplied by the Nutrivet Life Sciences, Pune was provided *ad libitum* from individual feeders on cage top. There were no known contaminants, which were reasonably expected to be in the dietary materials capable of interfering with the conduct of this study. The certificate of analysis provided by the supplier is appended to this final report.

Water:

Water was provided *ad libitum* from individual bottles attached to the cages. Water was from a local source and passed through the reverse osmosis membrane before use. There were no known contaminants, which were reasonably expected to be in the water capable of interfering with the conduct of this study. The routine analysis report is appended to this final report.

STUDY DESIGN

Route:

Oral (Gavage)

Justification for Route of Administration:

1) The dosage can be accurately administered;
2) It is the proposed route for clinical use;

Duration of the Study:

90 days consecutively and 4 week recovery period.

Experimental Design:

Group Number	Dose (mg/kg)	Treatment	Number of animals		Animal Number		Clinical Pathology		Histo-pathology
			Male	Female	Male	Female	Terminal	Reversal	
I	0	Vehicle	10	10	1-10	11-20	All survivals	-	All survivals
II	0	Vehicle (Reversal)	6	6	21-26	27-32	-	All survivals	-
III	250	Test Item	10	10	33-42	43-52	All survivals	-	-
IV	500		10	10	53-62	63-72	All survivals	-	-
V	1000		10	10	73-82	83-92	All survivals	-	All survivals
VI	1000	Test Item (Reversal)	6	6	93-98	99-104	-	All survivals	-

Justification for Dose Selection:

The doses for Main study were selected based on the results of the Acute Toxicity Study and Dose Range Finder study (IIT Study Number 17780, Acute Toxicity study date: 04-03-2014 to 21-03-2014 and IIT Study Number 17781, Dose Range Finder date: 03-06-2014 to 30-06-2014). The doses were selected in agreement with the Sponsor.

Administration of Test and / or Control Item:

The test and/or control item was administered by oral gavage route, using a 16 to 18 gauge ball–tipped intubation needle fitted onto a gauge syringe of appropriate size. Doses were calculated using recent body weights, 10 ml per kg of body weight was considered the maximum volume which could be administered to a rat.

Type and Frequency of Tests, Analyses and Measurements:

Viability:

Animals were observed twice daily.

Body Weights:

Body weights were recorded on the day of randomization, on the day of first dosing, weekly thereafter and a fasting body weight at scheduled sacrifice on day 91 and day 119.

Feed Consumption:

The quantity of feed consumed by control and different treatment groups was recorded on commencement of treatment and weekly thereafter until scheduled sacrifice and the feed consumption per animal was calculated for each group.

Ophthalmologic Examination:

The eyes of all the animals were examined prior to the initiation of the dosing and at scheduled sacrifice. Eye examination was carried out by using a HEINE mini 2000 ophthalmoscope for evaluation after the induction of mydriasis with 1% solution of tropicamide sulfate.

Clinical Observations and General Appearance:

Rats were examined once daily for clinical signs. Detailed clinical observations were made for individual animal once before the start of dose administration and at least once a week thereafter until scheduled sacrifice.

Detailed Clinical Observations:

Detailed clinical observations were made for all animals from treatment groups to assess the behavioral status of each animal. Detailed clinical observations were performed once before the start of dose administration and once a week thereafter until scheduled sacrifice.

a) Home Cage Observations:

In home cage, rats were observed for behavior, alterations, vocalizations, respiration and palpebral closer.

1) Behavior in Home cage:

The behavior of the rat was observed in home cage upon initial approach by the observer and description of behavior in home cage was recorded as:

1 = apparently sleeping.
2 = Awake, but immobile; apparently normal posture.
3 = Engaged in apparently normal movement such as rearing, drinking, or grooming.
4 = Immobile, with unusual posture or tonic convulsion (lying on side with legs extended, flattened body or arched back. (opisthotonos or emprosthonos).
5 = Unusual behaviour or muscular patterns (stereotyped behaviour such as head bobbing or weaving, circling, repetitive licking or grooming, bizarre behaviour such as self mutilation, writhing or retropulsion, unusual muscular patterns such as tremors, spasms or clonic convulsion).

2) Alterations Home cage:

The alterations of the rat were observed in home cage upon initial approach by the observer and description of alterations in home eage was recorded as:

1 = No alterations in behaviour or posture (Normal).
2 = Stereotyped behaviour pattern (head bobbing or weaving, circling, repetitive licking or grooming).
3 = Bizarre behaviours such as self-mutilation, writhing or retropulsion.
4 = Twitches or tremors in the limbs or repetitive movements of the mouth or jaws.
5 = Whole body tremors or spasms.
6 = Unusual posture (opisthotonos, emprosthotonos, tonic extension, head tilt, straub tail).
7 = Tonic-clonic seizure.

3) Vocalizations:

The occurrence of spontaneous or unprovoked vocalization was recorded as:

1= No vocalization/ Normal
2= Vocalization noted
If vocalization observed the actual number was recorded.

4) Respiration:

The observations for respiration were recorded as:

1 = Normal
2 = Abnormal
The type of abnormal respiration e.g. bradypnea, hyperpnea, dyspnea, rals was recorded in the clinical signs.

5) Palpebral closer:

The degree of closure of the eyelids was recorded as:
1 = Eyelids wide open (Normal).
2 = Eyelids slightly closed.
3 = Eyelids dropping, approximately half-closed.
4 = Eyelids completely shut.

b) Handling Observations:

After completing home cage observations, the rat was observed for reaction to removal, reaction to handling, urination, defecation, prominence of eye, lacrimation, salivation, piloerection, examination of mucous membrane, examination of skin / fur, examination of natural orifices and animal appearance.

1) Reaction to Removal:

The reaction of the rat removed from home cage was recorded as:
1 = Sits quietly and is easily removed.
2 = Vocalization without resistance to being picked up.
3 = Runs around cage with or without vocalization, or freezes or rears, following the investigator's hand.
4 = Tail and throat rattles, may attack.

2) Reaction to handling:

The reaction of the rat to handling from home cage was recorded as:
1 = Quiet with no resistance.
2 = Vocalization without resistance.
3 = Tense or rigid.
4 = Squirming and twisting, may attempt to bite.

3) Urination:

The frequency of urination was recorded as:
0 = No urination during the observation period.
1 = Urine present; quantity is not excessive.
2 = the amount of urination is excessive.

4) Defecation:

The frequency of defecation was recorded as:
0 = No defecation during the observation period.
1 = Fecal boluses have normal consistency.
2 = Soft or liquid feces.

5) Prominence of Eye:

The eyes were examined for prominence of eye and observation was recorded as:
1 = Normal
2 = Exophthalmos
3 = Enophthalmos

6) Lacrimation:

The degree of lacrimation was recorded as:
1 = No excess lacrimation (normal).
2 = Excess moisture at the margin of the eyelid.
3 = Persistent dampness at the margin of the eyelid
4 = Dampness extends beyond the margin of the eyelid.

7) Salivation:

The degree of salivation was recorded as:
1 = No excess salivation (normal).
2 = Margin of mouth wet.
3 = Wet zone ¼ to ½ of submandibular area.
4 = Wet zone extends to the entire submandibular area.

8) Piloerection:

Piloerection was differentiated from a scruffy or ungroomed coat by patting the back of the animal in a rostral to caudal direction. Piloerection was considered in case the animal hairs were erect after patting. The observation for piloerection was recorded as:

0 = Absent
1 = Present

9) Examination of Mucous Membrane:

The observation for visual mucous membrane was recorded as:

1 = Normal
2 = Abnormal (discolouration)

10) Examination of Skin / Fur:

The observation for skin / fur examination was recorded as:

1 = Normal
2 = Abnormal

11) Examination of Natural Orifices:

The observation for natural orifices examination was recorded as:

1 = Normal
2 = Abnormal

12) Animal Appearance:

The observation for appearanee of animal was recorded as:

1 = Clean and groomed.
2 = Unkempt (with scruffy and ungroomed coat)
3 = Stained by urine and/or feces.

c) Open field observation:

The animal was placed in the open field and its appearance and behavior were observed. The following observations were made and recorded:

1) Stereotype Behaviour:

The stereotype behaviour can be defined as the pronounced repetition of specific gesture or movements i.e. presence of excessive or repetitive behaviour that appears purposeless to the observer. The observation was recorded as:

0 = Absent
1 = Excessive grooming / licking / head bobbing or weaving
2 = Circling movements

2) Bizarre Behaviour:

The bizarre behaviour includes any unusual behaviour that will not be normally observed in the test species. The observation was recorded as:

0 = Absent
1 = Retropulsion
2 = Biting of cage
3 = Biting to other animal(s)
4 = Self destructive biting or mutilation

3) Rearing (Rears):

The number of times the rat raises both forelimbs off the surfaces is considered as rearing. The number of these actions was counted and total number of rearing was recorded.

4) Movements:

In the open field, each animal was observed for presence of clonic and tonic movements.

4.1) Clonic Movements:

The observation for clonic movement was recorded as:
0 = None /Normal
1 = repetitive mouth/jaw motion, such as, Chewing, clones of jaw
2 = Mild clonic tremors of whole body
3 = Repetitive clonic tremors/ seizure of whole body

4.2) Tonic Movements:

The observation for tonic movement was recorded as:
0 = None /Normal
1 = Contractions of limbs
2 =Unusual posture (Opisthotonos, Emprosthotonous, tonic extension, head tilt, straub tail).
3= seizure

5) Gait Pattern:

The gait pattern was evaluated by observing the movement of the rat in the open field and the observation was recorded as:
1 = Normal
2 = Ataxic
3 = Hind limbs or forelimbs show exaggerated or overcompensated movements, drag or appear splayed.
4 = Spastic
5 = Duck walk
6 = Scissor
7 = Hunched back

6) Mobility Score:

A measure of the ability of the animal to locomote despite gait abnormalities was recorded. The ranking of the degree of impairment of locomotion was recorded as:

1 = Normal
2 = Slightly impaired
3 = Totally impaired

7) Severity of Gait:

The severity of the gait abnormalities is graded and documented as follows:
1 = Slight gait abnormality
2 = Moderate gait abnormality
3 = Extreme gait abnormality

8) Pupillary response:

The animal eyes were briefly covered for 30 seconds with hand/cloth and then the penlight was pointed and the response to penlight was recorded as:

1 = Response
2 = No response

Functional Observation Battery:

Towards the end of the exposure period of 90 days, sensory reactivity to stimuli of different types (e.g. auditory, visual and proprioceptive stimuli) assessment of grip strength and motor activity assessment were conducted for all the animals (Group I, III, IV and V). Towards the end of the recovery period on day 118, sensory reactivity to stimuli of different types (e.g. auditory, visual and proprioceptive stimuli) assessment of grip strength and motor activity assessment were conducted for all the animals (Group II and VI).

Sensory Reactivity Observations:

Towards the end of the exposure period, sensory reactivity to stimuli of different types (e.g., auditory, visual and proprioceptive stimuli) was conducted for all the animals.

1) Arousal level:

The activity/arousal level of the animal was described during the observation period and is documented as follows:

1 = Very low (stuporous, comatose)
2 = Low (sluggish, some exploratory movement possible).
3 = Apparently normal (alert with exploratory movement).
4 = High (sudden startle, darting or freezing without apparent stimuli).
5 = Very high (sudden bouts of running, freezing with spontaneous vocalization).

2) Sensory Activity:

Sensory activity was assessed by following methods:

2.1) **Assessment of Visual Response**: A blunt probe was held approximately 4 cm away from front of the face / eye and moved away steadily and reaction was documented.

2.2) **Touch Response**: Avoiding the animal's field of vision, the rump was gently touched with blunt probe. The animals reaction to this stimulus was observed and was documented.

2.3) **Auditory Response**: Using a clicker approximately 5 cm above the back of the animal sudden sound was made. The animals reaction to this stimulus was observed and was documented.

2.4) **Tail Pinch Response:** The reaction to a tail pinch was rated (The tail pinch was applied by the blunt forceps at approximately 3 cm from the tip of tail. The reaction to tail pinch was observed and was documented.

All above four responses were graded as follows:

1 = No reaction.
2 = orientating response: Slowly turns towards the stimulus or walks away.
3 = Startle response or freezing reaction.
4 = More energetic response than "2" or "3".
5 = Jumps at or away, attack or bites.

3) Visual Placing Response:

The animal was removed from its cage and held at the base of the tail (holding the tail more distally can strip off the skin) then slowly lowered forward towards the edge of the observation area or another raised edge (such as the rim of an overturned cage). The visual placing response is graded and documented:

1 = Early extension of forelimbs to reach for the screen.
2 = Extends limbs only after contact with the vibrissae or nose.
3 = No extension even after contact with nose.

4) Air righting response:

Holding the animal in a supine position, it was dropped from approximately 30cm and the righting response was rated:

1 = Lands with all feet on the ground.
2 = Uncoordinated landing or lands on side.
3 = Lands on back.

Grip Strength:

Grip strength of fore limbs was measured with a digital grip strength meter (Columbus Instruments International Corporation, Ohio, USA) to determine the ability of the rat to grasp and hold on the mesh platform. The grip strength of each rat was measured in Kilogram (Kg) for 3 consecutive times and average of the three grip strength values was calculated.

Motor Activity:

Motor activity of each animal was monitored using an automated animal activity measuring system (Columbus Instruments, OPTO-M3, Ohio, USA). Animals were monitored for three consecutive 10 minutes intervals allowing for examination of both exploratory and acclimation activity levels. During this period, total and ambulatory activity of the animal was recorded. Stereotypic activity was calculated by subtracting ambulatory activity from total activity.

TERMINAL STUDIES

Clinical Laboratory Investigations

Blood samples (for haematology and biochemistry) were collected from all rats from each group at respective terminations.

Blood Collection: Samples of blood were withdrawn from the orbital sinus. Food was withheld overnight from all rats prior to sampling.

Anticoagulants: The blood samples were collected into tubes containing the following anticoagulants:

Potassium EDTA - for haematological investigations
Sodium Heparin - for biochemistry investigations
Sodium Citrate, 3.8% (100 µl/ml of blood for Prothrombin Time)

The blood samples collected within the Heparinised tubes were centrifuged at 3000 rpm for 10 minutes in order to separate the plasma.

Haematological and Clinical Biochemistry Investigations

Haematological and clinical chemistry investigations were performed on all rats scheduled to be sacrificed at the end of dosing period on day 91. The haematological and clinical chemistry investigations were performed on reversal group rats at termination of recovery period on day 119.

Haematological Investigations

Following haematological parameters were studied using Beckman Coulter haematology analyzer.

Hb : Hemoglobin (g/dL)
RBC : Red Blood Corpuscles (x 10^6 /µL)
HCT : Hematocrit (%)
MCV : Mean Corpuscular Volume (fL)
MCH : Mean Corpuscular Hemoglobin (pg)
MCHC : Mean Corpuscular Hemoglobin Concentration (g/dL)
Platelets (x 10^3 /µL)
WBC : White Blood Corpuscles (x 10^3 /µL)

Following investigations were done manually:
N : Neutrophils (%)
L : Lymphocytes (%)
E : Eosinophils (%)
M : Monocytes (%)
B : Basophil (%)
Pt. : Prothrombin time (sec.)

Clinical Biochemistry Investigations

Following biochemical parameters were studied using Dimension Xpand^{Plus} and Acculyte 5P.

Total Protein (g/dL)
Blood Urea Nitrogen (mg/dL)
Urea Nitrogen (mg/dL) Calculated
ALT : Alanine Aminotransferase (U/L)
AST : Aspartate Aminotransferase (U/L)
ALP : Alkaline Phosphatase (U/L)
GGT : Gamma Glutamyl Transferase (U/L)
Glucose (mg/dL)
Calcium (mmol/L)
Phosphorous (mg/dL)
Albumin (g/dL)
Total Bilirubin (mg/dL)
Creatinine (mmol/L)
Total Cholesterol (mg/dL)
Triglycerides (mg/dL)
Globulin (g/dL) Calculated
Sodium (mmol/L)
Potassium (mmol/L)
Chloride (mmol/L)

Urine Analyses

Urine analyses was performed on all rats scheduled sacrificed during the last week of dosing period. The urine analyses were performed on reversal group rats at termination of recovery period on day 119. The following estimations were performed using appropriate methodology as discussed below:

Rats were placed in metabolic cages and collection duration was approximately 16 hours.

Physical Examination:
Volume
Appearance
Colour

Chemical Examination:
The following estimations were performed using Urine analyses strips as discussed below :
pH
Specific Gravity
Proteins
Glucose
Ketones
Bilirubin
Urobililogen
Occult Blood
Nitrite

Pathology

Necropsy and Organ Weights

Method of Sacrifice

The rats were sacrificed by CO_2 asphyxiation.

Sacrifice - after 90 consecutive days of oral administration, all surviving study rats were sacrificed on day 91 (Group I, III, IV, V). In addition all rats from reversal groups were sacrificed on day 119 (Group II and VI).

Organ Weights

Liver, kidneys, adrenal glands, epididymides/uterus, thymus, spleen, brain, heart, ovaries/testes were dissected free of fat and weighed. The paired organs were weighed together.

Gross Pathology

All the rats surviving at the end of the treatment were sacrificed and gross lesions were noted.

Tissue Preservation and Histopathology

From each rat, samples or the whole of the tissues listed below were preserved. All tissues were fixed in 10% neutral buffered formalin except, eyes and testes of all animals were preserved in Davidson's solution for 24 hours and transferred to 10% neutral buffered formalin.

Procedure for preparation of slides of tissues of various organs from the rats of various dose groups were performed as per the standard operating procedures of Indian Institute of Toxicology, Pune.

Following tissue samples of organs from control and animals treated at different dose groups were preserved and those from control and treated at the highest dose level of 1000 mg/kg were subjected to histopathological examination.

Adrenals, Aorta, Brain (cerebrum, cerebellum and pons), Caecum, Colon, Duodenum, Epididymides, Eyes, Heart, Ileum, Jejunum, Kidneys, Liver, Lungs, Mesenteric Lymphnodes, Muscles - Skeletal muscle, Oesophagus, Ovaries, Pancreas, Pharyngeal Lymphnodes, Pituitary, Prostate, Rectum, Salivary Gland, Sciatic Nerve, Seminal Vesicles, Skin with Mammary Gland, Spleen, Spinal Cord (Cervical, mid thoracic and lumbar), Sternum with bone marrow, Stomach, Testes, Thymus, Trachea, Thyroid / Parathyroid, Urinary Bladder, Uterus.

Statistical Analysis

Raw data was processed and analyzed for reporting group means and standard deviations with significance between the controls and treated groups, using in-house developed statistical software. All the parameters characterized by continuous data such as body weight, per cent body weight change, feed consumption (calculated as gram per animal), organ weight, relative organ weight, haematological and clinical chemistry data were subjected to Bartlett's test to meet the homogeneity of variance before conducting Analysis of Variance (ANOVA) and Dunnett's t-test. Where the data was not meet the homogeneity of variance, Student's t-test were performed to calculate significance.

Significance was calculated at 1% as well as 5% level and indicated in the summary tables as follows:

* = Significant than control at 95% level of confidence ($p \leq 0.05$).
** = Significant than control at 99% level of confidence ($p \leq 0.01$).

Archives

All specimens (includes tissue bottles, tissue wax blocks, blood smears and histology slides), raw data and study related documents generated during the course of the study at Indian Institute of Toxicology, together with a copy of the final report will be lodged in the Indian Institute of Toxicology Archive.

Such specimens and records were retained for a period of nine years from the date of issue of the final report. At the end of the nine years retention period, the sponsor will be contacted and an advice may be sought on the future requirements.

Test Item Return

The laboratory has stored 1 gram of the test item as reserve test item (09-07-2014) in the archives of the Indian Institute of Toxicology, Pune for a period that provides for the characterization of the test item.

After completion of the study and submission of the final report, all unused samples of the test item was returned to the Sponsor using labels and shipping instructions provided by the Sponsor.

Animal Welfare

This study was performed as per the recommendations of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines for Laboratory Animal Facility published in The Gazette of India, December 15, 1998. CPCSEA registration number: 15/1999/CPCSEA.

RESULTS

DOSE RANGE FINDER

Viability (Table No.B)

Male and Female -

All animals from control and different dose groups survived throughout the dosing period of 28 days.

Body Weight (Table No.D; Appendix No.I)

Male and Female -

All animals from control and different dose groups exhibited normal body weight gain throughout the dosing period of 28 days.

Feed Consumption (Table No.E)

Male and Female -

Animals from control and different dose groups exhibited normal feed consumption at the end of the dosing period of 14 days.

Clinical Observations and General Appearance (Table No.C and Appendix No.II)

Male -

Group I (0 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 28 days (animal nos.1 to 6).

Group II (100 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 28 days (animal nos.13 to 18).

Group III (250 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 28 days (animal nos.25 to 30).

Group IV (500 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 28 days (animal nos.37 to 42).

Group V (1000 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 28 days (animal nos.49 to 54).

Female -

Group I (0 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 28 days (animal nos.7 to 12).

Group II (100 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 28 days (animal nos.19 to 24).

Group III (250 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 28 days (animal nos.31 to 36).

Group IV (500 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 28 days (animal nos.43 to 48).

Group V (1000 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 28 days (animal nos.55 to 60).

Haematological Investigations (Table No.F; Appendix No.III)

Male and Female -

Haematological investigations conducted at the end of dosing period on day 29, revealed no significant changes in the values of different parameters studied when compared with that of respective controls.

Clinical Biochemistry Investigations (Table No.G; Appendix No.IV)

Male and Female -

Biochemical investigations conducted at the end of dosing period on day 29, revealed following significant changes in the values of different parameters studied when compared with that of respective controls, however the increase/decreased in the values obtained was within normal biological and laboratory limits or the effect was not dose dependent.

Male :

Total Protein : Elevated levels were observed in animals from 100 mg/kg dose group, sacrificed on day 29 ($p \leq 0.05$),

Blood Urea Nitrogen and Alanine Aminotransferase : Elevated levels were observed in animals from 1000 mg/kg dose group, sacrificed on day 29 ($p \leq 0.01$),

Glucose : Elevated levels were observed in animals from 100 mg/kg ($p \leq 0.01$), 250 mg/kg ($p \leq 0.01$), 500 mg/kg ($p \leq 0.05$) and 1000 mg/kg ($p \leq 0.05$) dose groups, sacrificed on day 29 and

Aspartate Aminotransferase : Decreased levels were observed in animals from 500 mg/kg dose group, sacrificed on day 29 ($p \leq 0.01$),

Female :

Total Protein ($p \leq 0.01$) and Blood Urea Nitrogen ($p \leq 0.05$) : Elevated levels were observed in animals from 1000 mg/kg dose group, sacrificed on day 29.

Gross Pathology (Table No.H; Appendix No.V)

Gross pathological examination in male and female animals from control and different dose groups did not reveal any abnormality.

RESULTS

MAIN STUDY

Viability (Table No.I)

Male and Female -

All animals from control and different dose groups survived throughout the dosing period of 90 days and the post-dosing recovery period of 28 days.

Body Weight (Table No.J; Appendix No.VI; Figure No.V and VI)

Male -

Animals from control and different dose groups exhibited normal body weight gain throughout the dosing period of 90 days.

During the post-dosing recovery period, animals from 1000 mg/kg reversal group exhibited normal body weight gain when compared with that of control animals.

Female -

Animals from control and different dose groups exhibited normal body weight gain throughout the dosing period of 90 days.

During the post-dosing recovery period, animals from 1000 mg/kg reversal group exhibited normal body weight gain when compared with that of control animals.

Feed Consumption (Table No.K; Figure No.VII and VIII)

Male and Female -

Animals from control and different dose groups exhibited normal feed consumption at the end of the dosing period of 90 days.

Animals from control reversal and high reversal dose groups exhibited normal feed consumption at the end of the recovery period of 28 days.

Ophthalmoscopic Examination (Table No.L; Appendix No.VII)

No ocular abnormalities were observed on ophthalmological examination in the animals during pre-exposure and on day 90 and on day 118 (for reversal group animals).

Clinical Observations and General Appearance (Table No.M and Appendix No.VIII)

Male -

Group I (0 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days (animal nos.1 to 10).

Group II (0 mg/kg, Reversal): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days and during the post-dosing recovery period (animal nos.21 to 26).

Group III (250 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days (animal nos.33 to 42).

Group IV (500 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days (animal nos.53 to 62).

Group V (1000 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days (animal nos.73 to 82).

Group VI (1000 mg/kg, Reversal): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days and during the post-dosing recovery period (animal nos.93 to 98).

Female -

Group I (0 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days (animal nos.1 I to 20).

Group II (0 mg/kg, Reversal): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days and during the post-dosing recovery period (animal nos.27 to 32).

Group III (250 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days (animal nos.43 to 52).

Group IV (500 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days (animal nos.63 to 72).

Group V (1000 mg/kg): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days (animal nos.83 to 92).

Group VI (1000 mg/kg, Reversal): No clinical signs of toxicity were observed in the animals throughout the dosing period of 90 days and during the post-dosing recovery period (animal nos.99 to 104).

Detailed Clinical Observations (Tables No.N; Appendix No.IX)

Before commencement of treatment:

In home cage observation, rat from different dose groups and control group revealed normal behavior, alterations, vocalization, respiration and palpebral closer.

During handling observation, handling of rats did not reveal any abnormality from different dose groups and control group.

In the open field observation, rat did not reveal any abnormality from different dose groups and control group.

During treatment:

In home cage observation, rat from different dose groups and control group revealed normal behavior, alterations, vocalization, respiration and palpebral closer.

During handling observation, handling of rats did not reveal any abnormality from different dose groups and control group.

In the open field observation, rat did not reveal any abnormality from different dose groups and control group.

Detailed clinical observation did not reveal any abnormality in all groups during the dosing period of 90 days and during the post-dosing recovery period.

Functional Observations (Tables No.O; Appendix No.X, XI and XII)

Sensory Reactivity Observations:

All animals from control and different dose groups showed normal arousal level, visual response, touch response, auditory response, tail pinch response and visual placing response. Normal air righting reflex was observed in all animals from control and different dose groups in week 13.

Grip Strength:

Grip strength values observed in male and female animals for control and different dose groups were comparable.

Motor Activity:

Motor activity values observed in male and female animals for control and different dose groups were comparable.

Haematological Investigations (Table No.P; Appendix No.XIII)

Male and Female -

Haematological investigations conducted at the end of dosing period on day 91 and at the end of recovery period on day 119, revealed following significant changes in the values of different parameters studied when compared with that of respective controls, however the increase/decrease in the values obtained was within normal biological and laboratory limits or the effect was not dose dependent.

Male :

Hb ($p \leq 0.01$) and MCH ($p \leq 0.05$) : Decreased values were obtained for animals from 250 mg/kg dose group, sacrificed on day 91,

Hb ($p \leq 0.05$), HCT ($p \leq 0.05$) and Total WBC ($P \leq 0.01$) : Increased values were obtained for animals from 500 mg/kg dose group, sacrificed on day 91,

Neutrophils : Decreased values were obtained for animals from 1000 mg/kg reversal dose group, sacrificed on day 119 ($p \leq 0.05$) and

Lymphocytes : Increased values were obtained for animals from 1000 mg/kg reversal dose group, sacrificed on day 119 ($p \leq 0.05$).

Female :

MCV : Increased values were obtained for animals from 250 mg/kg dose group, sacrificed on day 91 ($p \leq 0.01$),

Total WBC : Increased values were obtained for animals from 500 mg/kg dose group, sacrificed on day 91 ($p \leq 0.01$),

Platelets : Decreased values were obtained for animals from 1000 mg/kg dose group, sacrificed on day 91 ($p \leq 0.01$),

Neutrophils : Decreased values were obtained for animals from 1000 mg/kg reversal dose group, sacrificed on day 119 ($p \leq 0.05$) and

Lymphocytes : Increased values were obtained for animals from 1000 mg/kg reversal dose group, sacrificed on day 119 ($p \leq 0.05$).

Clinical Biochemistry Investigations (Table No.Q; Appendix No.XIV)

Male and Female -

Biochemical investigations conducted at the end of dosing period on day 91 and at the end of recovery period on day 119, revealed following significant changes in the values of different parameters studied when compared with that of respective controls, however the increase/decreased in the values obtained was within normal biological and laboratory limits or the effect was not dose dependent.

Male :

Creatinine : Elevated levels were observed in animals from 500 mg/kg dose group, sacrificed on day 91 ($p \leq 0.01$),

Total Protein ($p \leq 0.05$) and Glucose ($p \leq 0.01$) : Decreased levels were observed in animals from 1000 mg/kg dose group, sacrificed on day 91,

Alanine Aminotransferase : Decreased levels were observed in animals from 250 mg/kg, 500 mg/kg and 1000 mg/kg dose groups, sacrificed on day 91 ($p \leq 0.05$),

Potassium : Elevated levels were observed in animals from 1000 mg/kg reversal dose group, sacrificed on day 119 ($p \leq 0.05$) and

Chloride : Decreased levels were observed in animals from 1000 mg/kg reversal dose group, sacrificed on day 119 ($p \leq 0.05$).

Female :

Total Protein, Globulin and Cholesterol : Elevated levels were observed in animals from 500 mg/kg dose group, sacrificed on day 91 ($p \leq 0.01$),

Aspartate Aminotransferase : Elevated levels were observed in animals from 500 mg/kg ($p \leq 0.01$) and 1000 mg/kg ($p \leq 0.05$) dose groups, sacrificed on day 91,

Creatinine : Elevated levels were observed in animals from 1000 mg/kg dose group, sacrificed on day 91 ($p \leq 0.05$),

Alkaline Phosphatase : Decreased levels were observed in animals from 250 mg/kg dose group, sacrificed on day 91 ($p \leq 0.05$),

Glucose : Decreased levels were observed in animals from 1000 mg/kg dose group, sacrificed on day 91 ($p \leq 0.05$),

Bilirubin : Decreased levels were observed in animals from 250 mg/kg and 1000 mg/kg dose groups, sacrificed on day 91 ($p \leq 0.01$),

Chloride : Decreased levels were observed in animals from 500 mg/kg ($p \leq 0.01$) and 1000 mg/kg ($p \leq 0.05$) dose groups, sacrificed on day 91 and

Globulin : Elevated levels were observed in animals from 1000 mg/kg reversal dose group, sacrificed on day 119 ($p \leq 0.05$).

Urine Analyses (Table No.R; Appendix No.XV)

Male and Female -

No statistically significant variation was observed in the urine analyses conducted at the end of the dosing period in week 13 and 17 (on day 86, 87, 88 and 119) in male and female animals of different dose groups as compared to control group animals.

Slightly higher volume of urine analysis was observed in female animals from 1000 mg/kg dose group.

Organ Weights (Table No.S, T; Appendix No.XVI, XVII)

Male -

In comparison with controls on day 91, organ weight data of animals from 500 mg/kg ($p \leq 0.05$) and 1000 mg/kg ($p \leq 0.01$) dose groups revealed increased relative weights of epididymides.

At the end of post-dosing recovery period on day 119, organ weight data of animals from 1000 mg/kg reversal group was found to be comparable.

Female -

In comparison with controls on day 91, organ weight data of animals from 500 mg/kg dose group revealed increased relative weights of adrenals ($p \leq 0.05$) and decreased relative weights of ovaries were observed in animals from 250 mg/kg dose group ($p \leq 0.05$).

At the end of post-dosing recovery period on day 119, organ weight data of animals from 1000 mg/kg reversal dose group revealed increased relative weights of spleen ($p \leq 0.05$).

Although significant changes in the values of organ weight was observed in male and female animals from different dose groups, no related gross pathological and histopathological findings were seen, hence these findings were considered to be of no toxicological importance.

Gross Pathology (Table No.U; Appendix No.XVIII)

Gross pathological examination on male and female animals from control and different dose groups did not reveal any abnormality.

Histopathology (Table No.V; Appendix No.XIX)

No treatment related histopathological changes were evident in male and female animals from control and high dose groups.

Histopathological examination revealed minimal, multifocal mononuclear cells infiltration in liver; minimal, multifocal interstitial haemorrhages and/or minimal, tubular dilatation and/or focal, mononuclear cells infiltration in the kidneys; minimal, multifocal haemosiderosis and/or diffuse congestion in spleen; minimal, multifocal alveolar haemorrhages and/or minimal, focal to multifocal histiocytosis in the lungs; minimal, diffuse dilatation of zona reticularis and/or minimal, multifocal vacuolation in zona fasiculata in the adrenals; minimal, luminal seminal coagulum in urinary bladder; minimal, diffuse luminal dilatation and/or diffuse, minimal infiltration of eosinophilic cells infiltration in the uterus; minimal, multifocal haemorrhages in thymus; presence of ultimobranchial cyst in thyroid; in male or female animals from control and high dose group. All the changes observed in the control and high dose treatment group animals were comparable and hence considered as incidental, physiological and mode of death related and are covered in the background historical data of the pathology.

REFERENCES

1) OECD Principles of Good Laboratory Practice: Document # 1, ENV/MC/CHEM (98)17 (revised in 1997).

2) OECD Guideline for the testing of Chemicals No. 408, "Repeated Dose-90 day Oral Toxicity Study in Rodents" adopted on 21st September, 1998.

3) Recommendations of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines for Laboratory Animal Facility published in The Gazette of India, December 15, 1998.

4) Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatment groups with a control. *J. Am. Stat. Assoc.* 50, pp. 1096-1121.

SECTION I

DOSE RANGE FINDER (28 DAY)

FIGURES, TABLES AND APPENDICES

FIG NO.I - MALE
GROUP MEAN BODY WEIGHTS (g)

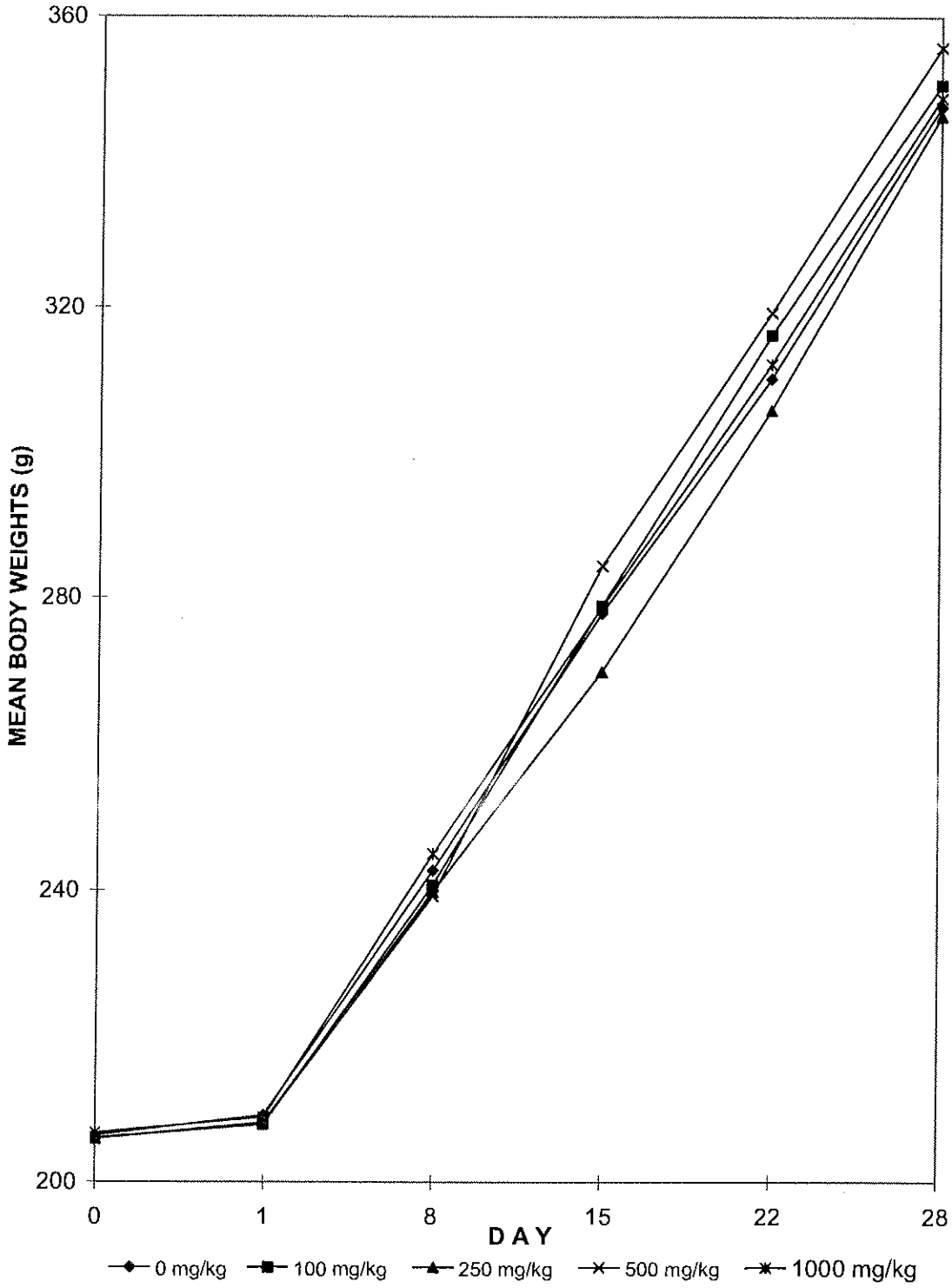

FIG NO.II - FEMALE
GROUP MEAN BODY WEIGHTS (g)

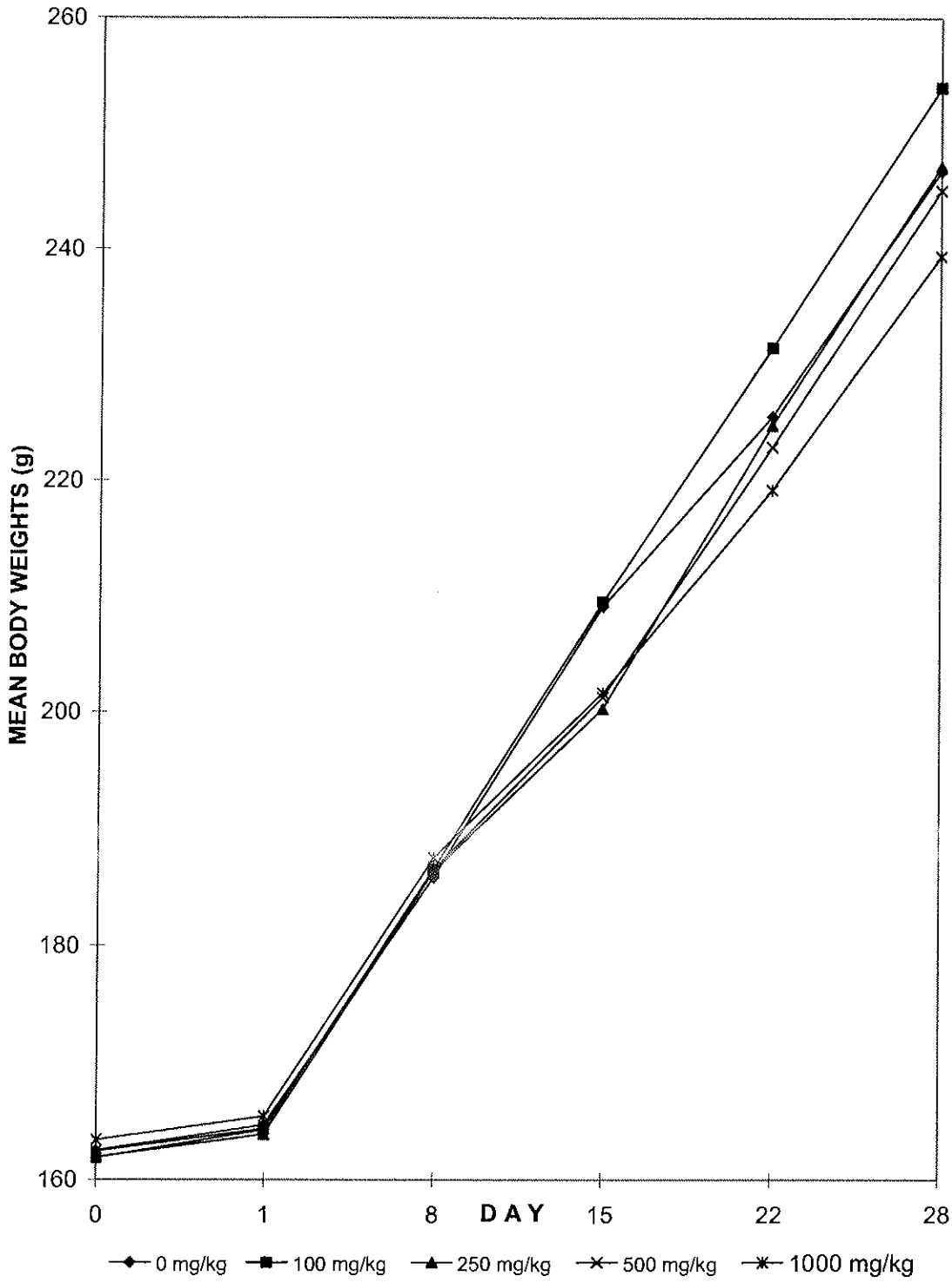

FIG NO.III - MALE
GROUP MEAN FEED CONSUMPTION (g/animal)

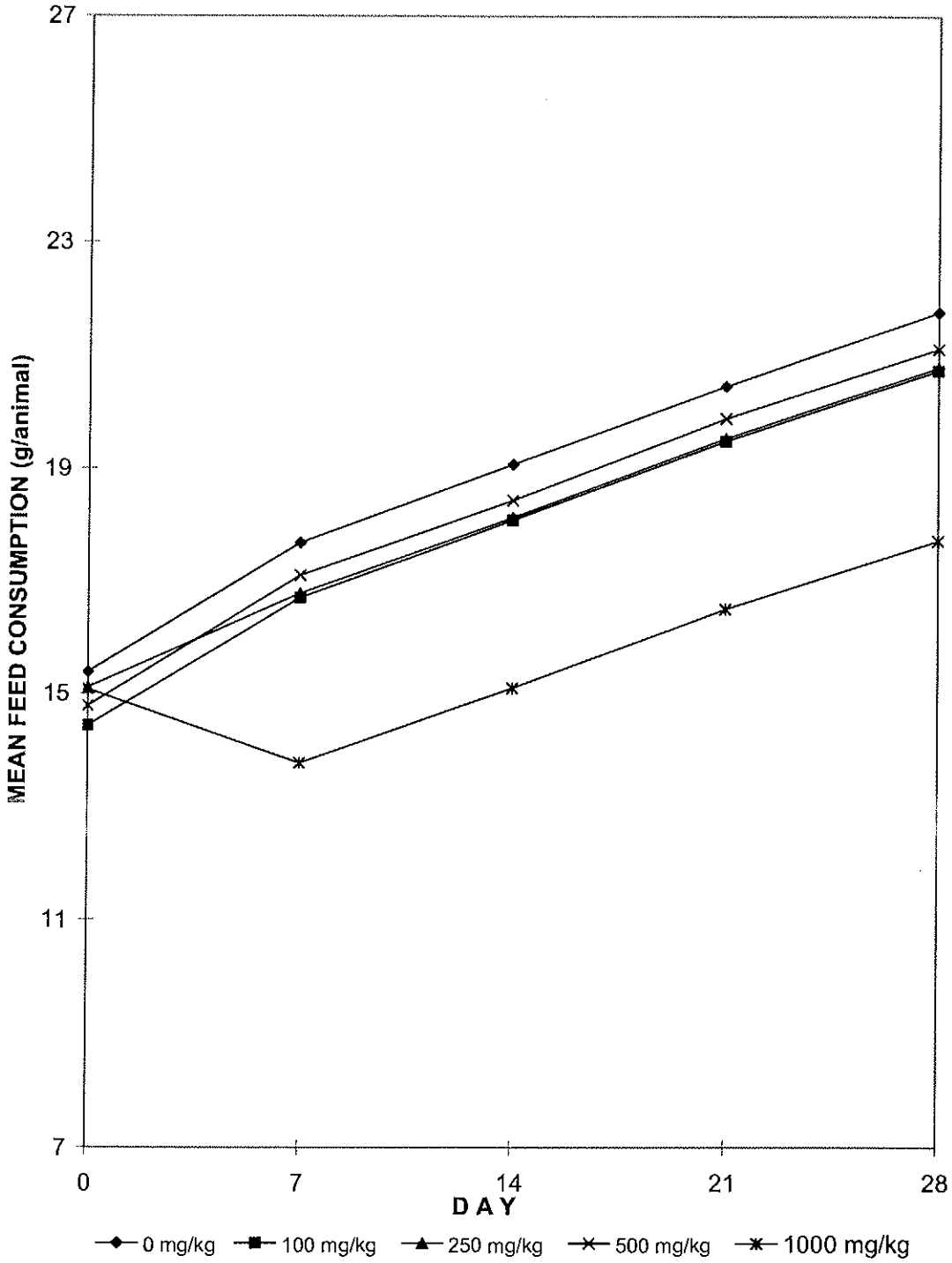

FIG NO.IV - FEMALE
GROUP MEAN FEED CONSUMPTION (g/animal)

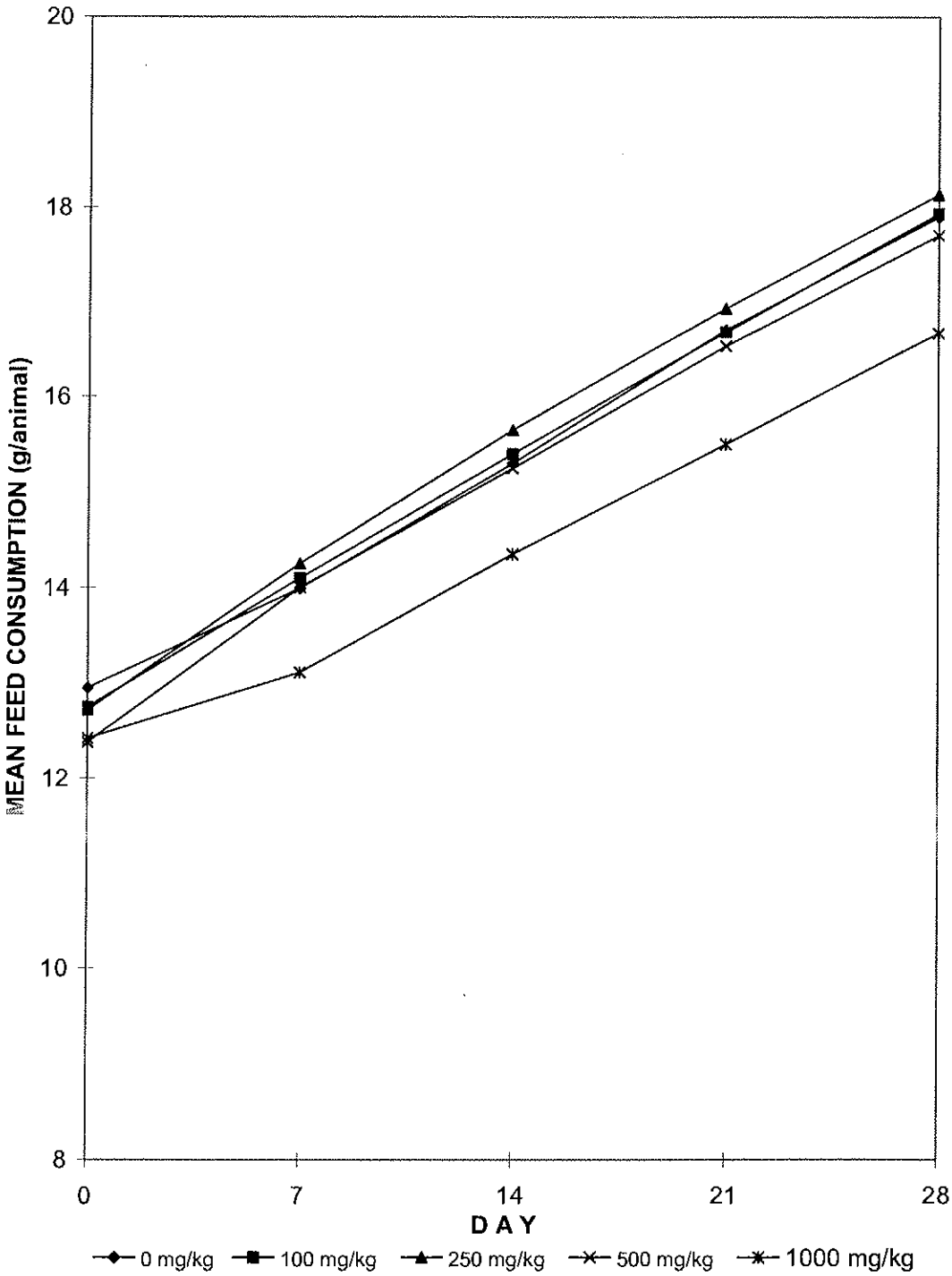

TABLE NO.A

ALLOCATION OF ANIMALS TO VARIOUS GROUPS

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Group Number	Dose mg/kg	Sex	Animal Numbers
I	0	Male	1 - 6
		Female	7 - 12
II	100	Male	13 - 18
		Female	19 - 24
III	250	Male	25 - 30
		Female	31 - 36
IV	500	Male	37 - 42
		Female	43 - 48
V	1000	Male	49 - 54
		Female	55 - 60

TABLE NO.B

VIABILITY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Under the conditions of the present study, the following mortality rates were recorded:

Group Number	Dose mg/kg		Mortality			
			Males		Females	
	Male	Female	Absolute	Relative %	Absolute	Relative %
I	0	0	0/6	0	0/6	0
II	100	100	0/6	0	0/6	0
III	250	250	0/6	0	0/6	0
IV	500	500	0/6	0	0/6	0
V	1000	1000	0/6	0	0/6	0

TABLE NO.C

SUMMARY OF CLINICAL OBSERVATIONS AND GENERAL APPEARANCE

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Day : 28

Group Number	Dose mg/kg	Observed Signs	Total Number of Animals	Animal Number	Period of signs in days from - to after dosing	Mortality
I	0	Nil	6	1 - 6	1 - 28	0/6
II	100	Nil	6	13 - 18	1 - 28	0/6
III	250	Nil	6	25 - 30	1 - 28	0/6
IV	500	Nil	6	37 - 42	1 - 28	0/6
V	1000	Nil	6	49 - 54	1 - 28	0/6

TABLE NO.C (Contd.)

SUMMARY OF CLINICAL OBSERVATIONS AND GENERAL APPEARANCE

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Day : 28

Group Number	Dose mg/kg	Observed Signs	Total Number of Animals	Animal Number	Period of signs in days from - to after dosing	Mortality
I	0	Nil	6	7 - 12	1 - 28	0/6
II	100	Nil	6	19 - 24	1 - 28	0/6
III	250	Nil	6	31 - 36	1 - 28	0/6
IV	500	Nil	6	43 - 48	1 - 28	0/6
V	1000	Nil	6	55 - 60	1 - 28	0/6

TABLE NO.D

GROUP MEAN BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex - Male

Group Number	Dose mg/kg		Day					
			0	1	8	15	22	28
I	0	Mean	206.43	209.20	242.70	277.82	310.07	347.63
		± SD	7.42	7.07	6.12	7.66	7.91	10.17
II	100	Mean	206.08	207.93	240.73	278.82	316.10	350.62
		± SD	5.43	5.63	9.93	9.39	18.10	20.41
III	250	Mean	205.97	208.20	239.78	269.78	305.73	346.37
		± SD	5.60	5.31	4.63	15.93	14.57	15.47
IV	500	Mean	205.97	208.13	239.23	284.28	319.23	355.80
		± SD	5.54	6.04	9.53	7.48	6.80	8.83
V	1000	Mean	206.75	208.92	244.97	278.60	312.07	348.82
		± SD	6.11	6.14	8.84	14.09	18.56	17.56

TABLE NO.D (Contd.)

GROUP MEAN BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex - Female

Group Number	Dose mg/kg		Day					
			0	1	8	15	22	28
I	0	Mean	162.53	164.70	185.83	209.10	225.48	246.73
		± SD	6.81	6.99	8.88	8.22	7.37	7.03
II	100	Mean	161.88	164.32	186.50	209.48	231.45	253.98
		± SD	6.10	6.15	4.77	3.35	6.24	7.09
III	250	Mean	161.95	163.90	186.32	200.25	224.73	247.18
		± SD	6.43	6.62	8.25	10.04	12.19	12.08
IV	500	Mean	162.47	164.38	186.45	201.23	222.85	245.07
		± SD	6.09	6.49	7.62	13.16	12.93	12.05
V	1000	Mean	163.43	165.45	187.47	201.62	219.15	239.37
		± SD	5.83	5.40	5.63	5.15	8.01	8.25

TABLE NO.E

GROUP MEAN FEED CONSUMPTION (g/animal)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex - Male

Group Number	Dose mg/kg		Day				
			0	7	14	21	28
I	0	Mean	15.38	17.68	19.07	20.45	21.76
II	100	Mean	14.43	16.70	18.08	19.48	20.73
III	250	Mean	15.11	16.78	18.13	19.53	20.78
IV	500	Mean	14.78	17.10	18.43	19.88	21.11
V	1000	Mean	15.08	13.77	15.10	16.50	17.72

TABLE NO.E (Contd.)

GROUP MEAN FEED CONSUMPTION (g/animal)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex - Female

Group Number	Dose mg/kg		Day				
			0	7	14	21	28
I	0	Mean	12.95	13.99	15.30	16.70	17.90
II	100	Mean	12.75	14.10	15.40	16.68	17.93
III	250	Mean	12.72	14.25	15.65	16.93	18.13
IV	500	Mean	12.38	14.00	15.25	16.53	17.70
V	1000	Mean	12.42	13.11	14.35	15.50	16.67

TABLE NO.F

GROUP MEAN HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Day : 29

Group Number	Dose mg/kg		Hb (g/dL)	Total RBC (x 10^6 /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
I	0	Mean	13.18	6.75	37.85	55.90	19.52	34.88
		± SD	1.72	0.71	5.52	2.20	0.70	0.64
II	100	Mean	14.08	7.07	39.97	56.37	19.87	35.27
		± SD	1.86	0.77	5.76	2.54	0.85	0.63
III	250	Mean	15.03	7.45	42.60	57.30	20.28	35.38
		± SD	1.51	0.90	4.88	2.68	1.06	0.73
IV	500	Mean	14.85	7.33	43.03	58.63	20.28	34.57
		± SD	1.66	0.73	5.06	2.34	0.82	0.33
V	1000	Mean	15.45	7.82	44.45	56.92	19.77	34.75
		± SD	1.94	1.01	5.66	2.29	0.89	0.53

Group Number	Dose mg/kg		Platelets (x 10^3 / µL)	Total WBC (x 10^3 /µL)	Differential %				
					N	L	E	M	B
I	0	Mean	553.50	16.37	20.17	77.50	1.50	0.83	0.00
		± SD	40.14	2.62	1.94	1.52	1.05	0.75	0.00
II	100	Mean	566.33	13.08	18.67	79.33	1.17	0.83	0.00
		± SD	43.42	1.03	2.73	3.88	1.17	0.75	0.00
III	250	Mean	578.83	14.93	18.33	79.33	1.50	0.83	0.00
		± SD	35.57	2.70	2.58	2.80	1.05	0.75	0.00
IV	500	Mean	568.33	15.90	19.00	78.67	1.17	1.17	0.00
		± SD	31.08	2.36	2.37	2.07	0.75	0.75	0.00
V	1000	Mean	596.50	14.37	18.67	79.17	1.00	1.17	0.00
		± SD	48.18	2.97	2.50	2.56	0.89	0.75	0.00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils

RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration

L : Lymphocytes
M : Monocytes

TABLE NO.F (Contd.)

GROUP MEAN HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Day : 29

Group Number	Dose mg/kg		Hb (g/dL)	Total RBC (x 10^6/µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
I	0	Mean	13.53	6.84	38.50	56.08	19.75	35.22
		± SD	2.11	0.79	5.92	2.08	0.83	0.66
II	100	Mean	15.48	7.80	44.85	57.27	19.80	34.62
		± SD	2.49	0.96	7.67	3.42	1.14	0.65
III	250	Mean	13.00	6.59	36.70	55.65	19.77	35.47
		± SD	0.86	0.30	2.54	2.41	0.97	0.47
IV	500	Mean	14.80	7.15	42.32	59.20	20.73	35.05
		± SD	1.11	0.56	3.65	1.22	0.43	0.44
V	1000	Mean	15.05	7.36	42.53	57.80	20.47	35.45
		± SD	0.95	0.50	3.15	2.33	0.76	0.45

Group Number	Dose mg/kg		Platelets (x 10^3 / µL)	Total WBC (x 10^3 /µL)	Differential %				
					N	L	E	M	B
I	0	Mean	552.17	15.90	18.67	80.00	0.83	0.50	0.00
		± SD	44.35	1.83	2.16	2.61	0.75	0.55	0.00
II	100	Mean	590.50	13.30	18.33	79.33	1.33	1.00	0.00
		± SD	43.21	4.46	3.61	4.32	1.21	0.63	0.00
III	250	Mean	539.83	14.63	20.17	77.67	0.83	1.33	0.00
		± SD	25.44	1.68	2.04	2.42	0.75	0.52	0.00
IV	500	Mean	569.17	15.33	17.50	80.00	1.17	1.33	0.00
		± SD	30.50	2.49	2.17	2.00	0.75	0.52	0.00
V	1000	Mean	565.83	15.10	18.50	79.17	1.17	1.17	0.00
		± SD	11.23	2.71	2.43	2.23	0.75	0.75	0.00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils
RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration
L : Lymphocytes
M : Monocytes

TABLE NO.G

GROUP MEAN CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Day : 29

Group Number	Dose mg/kg		Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
I	0	Mean	6.89	16.17	58.83	139.50	163.67	55.33
		± SD	0.16	1.17	2.64	6.66	21.04	6.86
II	100	Mean	7.69*	19.00	66.67	144.17	162.17	82.17**
		± SD	0.55	2.97	9.09	11.34	28.20	12.73
III	250	Mean	7.53	19.17	62.50	129.00	171.83	82.33**
		± SD	0.51	2.86	10.45	33.85	36.77	16.17
IV	500	Mean	7.27	18.83	59.67	119.17**	169.67	76.83*
		± SD	0.46	2.40	4.68	9.26	20.33	14.03
V	1000	Mean	6.94	20.17**	71.83**	141.17	174.00	64.67*
		± SD	0.41	2.79	7.86	24.33	25.71	5.96

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

* = Significant at 95% level of confidence ($p \leq 0.05$)
** = Significant at 99% level of confidence ($p \leq 0.01$)

TABLE NO.G (Contd.)

GROUP MEAN CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Day : 29

Group Number	Dose mg/kg		Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
I	0	Mean	6.93	17.50	51.33	124.67	107.83	65.83
		± SD	0.33	2.66	5.39	13.28	16.51	9.58
II	100	Mean	7.79	20.17	59.17	140.17	95.50	72.83
		± SD	0.47	3.76	7.65	13.32	33.38	6.79
III	250	Mean	8.13	21.50	52.17	130.00	95.00	74.33
		± SD	0.60	3.45	8.04	16.58	27.42	7.63
IV	500	Mean	8.08	22.33	51.50	150.00	123.17	64.00
		± SD	0.54	4.80	7.42	16.05	24.91	4.69
V	1000	Mean	7.81**	23.17*	50.17	136.67	109.50	68.50
		± SD	0.25	5.42	5.04	12.14	20.82	9.52

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

* = Significant at 95% level of confidence ($p \leq 0.05$)
** = Significant at 99% level of confidence ($p \leq 0.01$)

TABLE NO.H

SUMMARY OF GROSS PATHOLOGY FINDINGS

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Site and lesion observed	Group Number	I	II	III	IV	V
	Dose (mg/kg)	0	100	250	500	1000
No Abnormality Detected		1 - 6	13 - 18	25 - 30	37 - 42	49 - 54

Sex : Female

Site and lesion observed	Group Number	I	II	III	IV	V
	Dose (mg/kg)	0	100	250	500	1000
No Abnormality Detected		7 - 12	19 - 24	31 - 36	43 - 48	55 - 60

APPENDIX NO.I

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : I

Dose : 0 mg/kg

Animal Number	Day					
	0	1	8	15	22	28
1	195.8	199.0	238.1	273.1	296.5	329.3
2	202.8	205.8	235.1	268.4	317.7	355.6
3	204.5	207.9	244.7	275.1	309.6	354.3
4	207.7	210.5	240.3	276.3	306.3	343.6
5	209.9	211.6	245.9	285.6	316.6	355.2
6	217.9	220.4	252.1	288.4	313.7	347.8

APPENDIX NO.I (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : I

Dose : 0 mg/kg

Animal Number	Day					
	0	1	8	15	22	28
7	151.5	153.3	172.2	198.4	218.4	240.5
8	159.6	161.4	180.2	201.0	218.4	242.8
9	162.0	164.2	184.0	208.3	225.6	246.9
10	164.6	166.9	189.2	212.5	224.3	241.5
11	165.6	168.6	193.1	214.5	227.9	249.4
12	171.9	173.8	196.3	219.9	238.3	259.3

APPENDIX NO.I (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : II

Dose : 100 mg/kg

Animal Number	Day					
	0	1	8	15	22	28
13	198.8	200.3	224.3	265.3	297.9	332.3
14	200.9	202.8	235.1	271.7	305.8	326.8
15	205.1	206.9	241.1	277.9	304.2	343.6
16	208.7	210.2	243.8	280.4	316.6	360.7
17	210.7	212.9	248.1	290.3	347.5	381.7
18	212.3	214.5	252.0	287.3	324.6	358.6

APPENDIX NO.I (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : II

Dose : 100 mg/kg

Animal Number	Day					
	0	1	8	15	22	28
19	152.7	155.2	180.8	204.3	220.8	243.3
20	156.7	158.7	184.4	207.8	230.9	253.1
21	162.4	164.7	189.1	211.4	239.0	264.0
22	164.6	167.5	182.0	208.3	229.1	249.8
23	165.8	168.9	190.2	211.4	233.9	255.9
24	169.1	170.9	192.5	213.7	235.0	257.8

APPENDIX NO.I (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : III

Dose : 250 mg/kg

Animal Number	Day					
	0	1	8	15	22	28
25	199.4	202.2	234.7	274.5	316.7	361.1
26	201.1	203.2	238.7	273.8	305.4	346.9
27	202.9	205.6	234.3	264.2	300.6	348.0
28	208.5	210.7	245.0	268.7	301.9	340.6
29	210.8	212.1	242.0	293.2	326.1	361.8
30	213.1	215.4	244.0	244.3	283.7	319.8

APPENDIX NO.I (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : III

Dose : 250 mg/kg

Animal Number	Day					
	0	1	8	15	22	28
31	152.6	154.5	173.4	200.3	222.3	244.6
32	157.8	159.0	185.2	187.7	210.2	232.2
33	159.5	162.0	181.3	194.3	217.8	241.3
34	164.9	166.3	188.8	213.3	234.3	255.1
35	167.3	169.8	193.3	195.0	220.0	243.1
36	169.6	171.8	195.9	210.9	243.8	266.8

APPENDIX NO.I (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : IV

Dose : 500 mg/kg

Animal Number	Day					
	0	1	8	15	22	28
37	199.8	201.7	235.1	285.4	322.0	359.9
38	201.7	202.7	222.6	274.2	308.9	339.9
39	203.4	205.9	242.3	275.7	312.9	354.6
40	205.8	208.1	245.0	290.6	325.2	363.2
41	211.1	213.4	240.4	290.0	321.0	353.7
42	214.0	217.0	250.0	289.8	325.4	363.5

APPENDIX NO.I (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : IV

Dose : 500 mg/kg

Animal Number	Day					
	0	1	8	15	22	28
43	153.2	154.9	176.1	195.4	216.9	240.4
44	158.7	160.1	178.2	181.7	202.2	225.0
45	161.8	162.8	188.1	193.2	218.2	242.4
46	163.6	165.9	190.3	215.4	234.6	255.8
47	167.2	170.3	195.4	210.9	236.1	257.9
48	170.3	172.3	190.6	210.8	229.1	248.9

APPENDIX NO.I (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : V

Dose : 1000 mg/kg

Animal Number	Day					
	0	1	8	15	22	28
49	200.5	203.6	238.3	254.6	287.8	323.0
50	201.5	204.5	240.4	278.1	302.5	343.9
51	204.5	205.1	237.6	286.6	328.2	365.0
52	206.2	207.9	243.7	294.7	309.3	345.6
53	211.4	213.1	248.9	272.0	305.5	343.2
54	216.4	219.3	260.9	285.6	339.1	372.2

APPENDIX NO.I (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : V

Dose : 1000 mg/kg

Animal Number	Day					
	0	1	8	15	22	28
55	155.3	157.2	180.6	192.6	212.3	233.9
56	159.5	161.9	184.7	206.9	233.0	252.5
57	162.2	165.2	186.6	201.5	215.3	234.1
58	164.1	166.9	184.5	201.3	220.1	239.5
59	167.9	168.9	192.9	201.0	211.7	230.8
60	171.6	172.6	195.5	206.4	222.5	245.4

APPENDIX NO.II

INDIVIDUAL ANIMAL - CLINICAL OBSERVATIONS AND GENERAL APPEARANCE

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number	Dose mg/kg	Animal Number	Observed Signs	Period of signs in days from - to after dosing
I	0	1	Nil	1 - 28
		2	Nil	1 - 28
		3	Nil	1 - 28
		4	Nil	1 - 28
		5	Nil	1 - 28
		6	Nil	1 - 28
II	100	13	Nil	1 - 28
		14	Nil	1 - 28
		15	Nil	1 - 28
		16	Nil	1 - 28
		17	Nil	1 - 28
		18	Nil	1 - 28
III	250	25	Nil	1 - 28
		26	Nil	1 - 28
		27	Nil	1 - 28
		28	Nil	1 - 28
		29	Nil	1 - 28
		30	Nil	1 - 28
IV	500	37	Nil	1 - 28
		38	Nil	1 - 28
		39	Nil	1 - 28
		40	Nil	1 - 28
		41	Nil	1 - 28
		42	Nil	1 - 28
V	1000	49	Nil	1 - 28
		50	Nil	1 - 28
		51	Nil	1 - 28
		52	Nil	1 - 28
		53	Nil	1 - 28
		54	Nil	1 - 28

APPENDIX NO.II (Contd.)

INDIVIDUAL ANIMAL - CLINICAL OBSERVATIONS AND GENERAL APPEARANCE

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number	Dose mg/kg	Animal Number	Observed Signs	Period of signs in days from - to after dosing
I	0	7	Nil	1 - 28
		8	Nil	1 - 28
		9	Nil	1 - 28
		10	Nil	1 - 28
		11	Nil	1 - 28
		12	Nil	1 - 28
II	100	19	Nil	1 - 28
		20	Nil	1 - 28
		21	Nil	1 - 28
		22	Nil	1 - 28
		23	Nil	1 - 28
		24	Nil	1 - 28
III	250	31	Nil	1 - 28
		32	Nil	1 - 28
		33	Nil	1 - 28
		34	Nil	1 - 28
		35	Nil	1 - 28
		36	Nil	1 - 28
IV	500	43	Nil	1 - 28
		44	Nil	1 - 28
		45	Nil	1 - 28
		46	Nil	1 - 28
		47	Nil	1 - 28
		48	Nil	1 - 28
V	1000	55	Nil	1 - 28
		56	Nil	1 - 28
		57	Nil	1 - 28
		58	Nil	1 - 28
		59	Nil	1 - 28
		60	Nil	1 - 28

APPENDIX NO.III

INDIVIDUAL ANIMAL - HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : I

Dose : 0 mg/kg

Day : 29

Animal Number	Hb (g/dL)	Total RBC ($x 10^6$ /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
1	12.5	6.57	35.7	54.3	19.0	34.9
2	11.8	6.23	33.9	54.4	19.0	34.9
3	16.2	8.11	48.1	59.2	20.0	33.7
4	14.3	6.91	40.2	58.2	20.7	35.5
5	12.2	6.42	34.9	54.4	19.0	34.9
6	12.1	6.24	34.3	54.9	19.4	35.4

Animal Number	Platelets ($x 10^3$ / µL)	Total WBC ($x 10^3$ /µL)	Differential %				
			N	L	E	M	B
1	548	19.2	17	80	02	01	00
2	531	17.8	20	77	03	00	00
3	628	12.8	22	76	02	00	00
4	563	14.0	19	78	01	02	00
5	538	18.7	22	76	01	01	00
6	513	15.7	21	78	00	01	00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils

RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration

L : Lymphocytes
M : Monocytes

APPENDIX NO.III (Contd.)

INDIVIDUAL ANIMAL - HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : I

Dose : 0 mg/kg

Day : 29

Animal Number	Hb (g/dL)	Total RBC ($\times 10^6$ /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
7	12.4	6.58	36.0	54.6	18.9	34.6
8	12.1	6.39	35.0	54.7	18.9	34.5
9	14.6	7.15	41.7	58.4	20.5	35.1
10	12.4	6.39	35.1	54.9	19.4	35.4
11	17.4	8.32	49.2	59.1	20.9	35.4
12	12.3	6.21	34.0	54.8	19.9	36.3

Animal Number	Platelets ($\times 10^3$ / µL)	Total WBC ($\times 10^3$ /µL)	Differential %				
			N	L	E	M	B
7	544	19.0	19	79	02	00	00
8	526	15.5	16	84	00	00	00
9	571	14.1	22	77	01	00	00
10	525	16.5	20	78	01	01	00
11	633	14.1	17	82	00	01	00
12	514	16.2	18	80	01	01	00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils

RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration

L : Lymphocytes
M : Monocytes

APPENDIX NO.III (Contd.)

INDIVIDUAL ANIMAL - HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : II

Dose : 100 mg/kg

Day : 29

Animal Number	Hb (g/dL)	Total RBC ($\times 10^6$ /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
13	12.3	6.65	34.9	52.5	18.5	35.2
14	14.1	6.76	39.5	58.4	20.9	35.8
15	17.4	8.56	50.6	59.1	20.3	34.3
16	14.5	7.17	40.4	56.3	20.2	35.9
17	12.4	6.40	34.8	54.3	19.3	35.6
18	13.8	6.88	39.6	57.6	20.0	34.8

Animal Number	Platelets ($\times 10^3$ / µL)	Total WBC ($\times 10^3$ /µL)	Differential %				
			N	L	E	M	B
13	510	13.4	19	77	02	02	00
14	557	13.9	23	73	03	01	00
15	634	12.9	20	80	00	00	00
16	592	11.6	17	82	01	00	00
17	536	14.4	18	80	01	01	00
18	569	12.3	15	84	00	01	00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils

RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration

L : Lymphocytes
M : Monocytes

APPENDIX NO.III (Contd.)

INDIVIDUAL ANIMAL - HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : II

Dose : 100 mg/kg

Day : 29

Animal Number	Hb (g/dL)	Total RBC ($\times 10^6$ /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
19	18.5	8.99	55.1	61.3	20.6	33.6
20	12.3	6.81	35.6	52.3	18.1	34.6
21	17.8	8.57	50.7	59.1	20.7	35.1
22	14.3	7.68	41.5	54.0	18.6	34.5
23	13.5	6.57	38.0	57.8	20.5	35.5
24	16.5	8.15	48.2	59.1	20.3	34.4

Animal Number	Platelets ($\times 10^3$ / µL)	Total WBC ($\times 10^3$ /µL)	Differential %				
			N	L	E	M	B
19	620	18.4	15	84	00	01	00
20	525	13.5	19	78	02	01	00
21	632	5.5	24	75	01	00	00
22	570	16.8	14	85	00	01	00
23	567	12.9	18	79	02	01	00
24	629	12.7	20	75	03	02	00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils

RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration

L : Lymphocytes
M : Monocytes

APPENDIX NO.III (Contd.)

INDIVIDUAL ANIMAL - HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : III

Dose : 250 mg/kg

Day : 29

Animal Number	Hb (g/dL)	Total RBC ($\times 10^6$ /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
25	15.9	7.44	45.4	61.0	21.4	35.1
26	15.2	7.52	42.2	56.2	20.3	36.1
27	14.8	7.01	41.9	59.8	21.1	35.3
28	13.4	6.41	36.8	57.4	20.9	36.4
29	13.5	7.20	38.8	53.9	18.8	34.9
30	17.4	9.10	50.5	55.5	19.2	34.5

Animal Number	Platelets ($\times 10^3$ / µL)	Total WBC ($\times 10^3$ /µL)	Differential %				
			N	L	E	M	B
25	573	16.8	18	79	03	00	00
26	595	11.8	23	74	02	01	00
27	555	18.4	16	81	01	02	00
28	548	13.3	19	80	00	01	00
29	559	16.7	16	82	01	01	00
30	643	12.6	18	80	02	00	00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils

RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration

L : Lymphocytes
M : Monocytes

APPENDIX NO.III (Contd.)

INDIVIDUAL ANIMAL - HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : III

Dose : 250 mg/kg

Day : 29

Animal Number	Hb (g/dL)	Total RBC ($\times 10^6$ /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
31	12.2	6.36	34.5	54.1	19.2	35.5
32	14.1	6.82	39.8	58.3	20.7	35.5
33	13.1	6.42	37.0	57.6	20.5	35.5
34	11.8	6.27	32.9	52.5	18.8	35.7
35	13.2	7.05	38.1	54.0	18.7	34.6
36	13.6	6.60	37.9	57.4	20.7	36.0

Animal Number	Platelets ($\times 10^3$ / µL)	Total WBC ($\times 10^3$ /µL)	Differential %				
			N	L	E	M	B
31	531	16.6	23	74	01	02	00
32	561	13.6	21	76	02	01	00
33	548	12.8	17	81	01	01	00
34	495	13.2	19	78	01	02	00
35	539	16.5	21	78	00	01	00
36	565	15.1	20	79	00	01	00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils

RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration

L : Lymphocytes
M : Monocytes

APPENDIX NO.III (Contd.)

INDIVIDUAL ANIMAL - HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : IV

Dose : 500 mg/kg

Day : 29

Animal Number	Hb (g/dL)	Total RBC ($x 10^6$ /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
37	17.4	8.68	51.2	58.9	20.0	34.0
38	12.6	6.72	36.4	54.2	18.8	34.7
39	14.9	7.30	42.6	58.4	20.5	35.0
40	14.4	7.00	41.7	59.6	20.6	34.5
41	15.9	7.53	45.9	61.0	21.2	34.7
42	13.9	6.77	40.4	59.7	20.6	34.5

Animal Number	Platelets ($x 10^3$ / µL)	Total WBC ($x 10^3$ /µL)	Differential %				
			N	L	E	M	B
37	621	12.4	17	81	02	00	00
38	543	17.3	20	78	01	01	00
39	573	13.4	18	79	01	02	00
40	547	17.8	22	77	00	01	00
41	584	16.9	21	76	02	01	00
42	542	17.6	16	81	01	02	00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils

RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration

L : Lymphocytes
M : Monocytes

APPENDIX NO.III (Contd.)

INDIVIDUAL ANIMAL - HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : IV

Dose : 500 mg/kg

Day : 29

Animal Number	Hb (g/dL)	Total RBC ($x 10^6$ /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
43	14.6	7.17	41.7	58.2	20.4	35.1
44	16.3	8.06	47.5	58.9	20.2	34.3
45	13.3	6.50	37.4	57.6	20.5	35.6
46	14.3	6.85	40.9	59.7	20.9	35.1
47	15.9	7.48	45.6	61.0	21.3	34.9
48	14.4	6.83	40.8	59.8	21.1	35.3

Animal Number	Platelets ($x 10^3$ / µL)	Total WBC ($x 10^3$ /µL)	Differential %				
			N	L	E	M	B
43	570	13.4	15	82	02	01	00
44	626	12.7	17	79	02	02	00
45	557	13.2	15	83	01	01	00
46	549	17.9	19	79	01	01	00
47	573	16.8	20	78	00	02	00
48	540	18.0	19	79	01	01	00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils

RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration

L : Lymphocytes
M : Monocytes

APPENDIX NO.III (Contd.)

INDIVIDUAL ANIMAL - HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : V

Dose : 1000 mg/kg

Day : 29

Animal Number	Hb (g/dL)	Total RBC ($\times 10^6$ /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
49	16.4	8.74	48.6	55.6	18.8	33.8
50	17.9	8.61	50.9	59.1	20.7	35.1
51	13.8	7.34	39.6	54.0	18.8	34.7
52	13.2	6.52	37.4	57.4	20.2	35.3
53	14.3	6.91	41.4	59.9	20.7	34.6
54	17.1	8.78	48.8	55.5	19.4	35.0

Animal Number	Platelets ($\times 10^3$ / µL)	Total WBC ($\times 10^3$ /µL)	Differential %				
			N	L	E	M	B
49	651	11.9	19	78	02	01	00
50	629	13.0	21	78	01	00	00
51	565	18.6	20	78	00	02	00
52	557	12.8	20	77	02	01	00
53	539	17.7	18	80	01	01	00
54	638	12.2	14	84	00	02	00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils

RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration

L : Lymphocytes
M : Monocytes

APPENDIX NO.III (Contd.)

INDIVIDUAL ANIMAL - HAEMATOLOGY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : V

Dose : 1000 mg/kg

Day : 29

Animal Number	Hb (g/dL)	Total RBC ($\times 10^6$ /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
55	14.2	7.12	40.1	56.3	19.9	35.4
56	15.7	7.40	44.9	60.7	21.2	34.9
57	16.4	8.04	47.0	58.4	20.4	35.0
58	13.8	6.65	38.3	57.6	20.8	36.1
59	15.2	7.18	42.8	59.6	21.2	35.6
60	15.0	7.78	42.1	54.2	19.3	35.7

Animal Number	Platelets ($\times 10^3$ / µL)	Total WBC ($\times 10^3$ /µL)	Differential %				
			N	L	E	M	B
55	582	11.7	17	80	02	01	00
56	576	16.2	19	80	01	00	00
57	567	13.5	22	76	00	02	00
58	559	13.4	18	80	01	01	00
59	554	19.1	20	77	02	01	00
60	557	16.7	15	82	01	02	00

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils

RBC : Red Blood Corpuscules
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration

L : Lymphocytes
M : Monocytes

APPENDIX NO.IV

INDIVIDUAL ANIMAL - CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : I

Dose : 0 mg/kg

Day : 29

Animal Number	Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
1	6.61	17	57	132	174	58
2	6.80	16	62	133	166	63
3	6.89	14	58	137	187	62
4	7.01	17	55	148	177	48
5	7.03	16	61	146	148	54
6	7.01	17	60	141	130	47

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

APPENDIX NO.IV (Contd.)

INDIVIDUAL ANIMAL - CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : I

Dose : 0 mg/kg

Day : 29

Animal Number	Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
7	6.56	17	52	119	97	67
8	6.82	19	59	147	130	56
9	6.86	13	51	134	84	56
10	6.81	18	55	119	105	67
11	6.99	17	47	111	121	67
12	7.53	21	44	118	110	82

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

APPENDIX NO.IV (Contd.)

INDIVIDUAL ANIMAL - CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : II

Dose : 100 mg/kg

Day : 29

Animal Number	Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
13	7.97	17	60	144	205	85
14	8.36	20	62	130	123	87
15	7.87	24	65	145	162	88
16	7.81	20	83	159	181	96
17	6.78	17	59	133	152	78
18	7.34	16	71	154	150	59

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

APPENDIX NO.IV (Contd.)

INDIVIDUAL ANIMAL - CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : II

Dose : 100 mg/kg

Day : 29

Animal Number	Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
19	7.42	26	70	163	79	73
20	7.85	16	58	123	79	77
21	7.38	23	48	138	64	60
22	7.46	19	62	144	111	72
23	8.07	17	63	140	156	76
24	8.56	20	54	133	84	79

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

APPENDIX NO.IV (Contd.)

INDIVIDUAL ANIMAL - CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : III

Dose : 250 mg/kg

Day : 29

Animal Number	Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
25	7.36	17	57	121	130	64
26	7.04	16	57	122	186	101
27	8.04	24	70	184	228	103
28	7.96	20	79	113	167	81
29	6.88	20	50	85	186	73
30	7.92	18	62	149	134	72

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

APPENDIX NO.IV (Contd.)

INDIVIDUAL ANIMAL - CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : III

Dose : 250 mg/kg

Day : 29

Animal Number	Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
31	8.25	17	56	133	146	65
32	7.53	22	62	141	82	65
33	7.30	19	38	103	96	80
34	8.67	21	51	145	81	76
35	8.78	27	55	141	98	83
36	8.25	23	51	117	67	77

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

APPENDIX NO.IV (Contd.)

INDIVIDUAL ANIMAL - CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : IV

Dose : 500 mg/kg

Day : 29

Animal Number	Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
37	7.25	23	53	121	138	64
38	7.50	19	56	129	177	100
39	6.60	17	58	110	167	88
40	6.95	17	63	113	179	68
41	7.36	20	64	111	159	71
42	7.95	17	64	131	198	70

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

APPENDIX NO.IV (Contd.)

INDIVIDUAL ANIMAL - CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : IV

Dose : 500 mg/kg

Day : 29

Animal Number	Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
43	7.51	21	54	161	95	57
44	7.96	19	55	150	120	69
45	8.37	32	48	133	92	60
46	8.67	21	40	139	143	68
47	7.40	21	50	141	148	64
48	8.54	20	62	176	141	66

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

APPENDIX NO.IV (Contd.)

INDIVIDUAL ANIMAL - CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : V

Dose : 1000 mg/kg

Day : 29

Animal Number	Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
49	6.98	21	69	136	138	58
50	6.76	23	72	113	172	59
51	6.38	16	59	126	170	65
52	6.92	18	75	131	168	73
53	6.94	20	73	164	218	63
54	7.64	23	83	177	178	70

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

APPENDIX NO.IV (Contd.)

INDIVIDUAL ANIMAL - CLINICAL BIOCHEMISTRY

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : V

Dose : 1000 mg/kg

Day : 29

Animal Number	Total Protein (g/dL)	BUN (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
55	7.88	30	44	128	89	65
56	7.68	19	54	157	107	64
57	7.73	30	45	125	93	60
58	7.45	19	50	141	116	69
59	7.93	22	51	128	105	87
60	8.17	19	57	141	147	66

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Transaminase
ALP : Alkaline Phosphatase

APPENDIX NO.V

INDIVIDUAL ANIMAL - GROSS PATHOLOGY FINDINGS

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Day on Test : 29

Group Number	Dose mg/kg	Animal Number	Animal Fate	Gross pathology findings
I	0	1	TS	No Abnormality Detected
		2	TS	No Abnormality Detected
		3	TS	No Abnormality Detected
		4	TS	No Abnormality Detected
		5	TS	No Abnormality Detected
		6	TS	No Abnormality Detected
II	100	13	TS	No Abnormality Detected
		14	TS	No Abnormality Detected
		15	TS	No Abnormality Detected
		16	TS	No Abnormality Detected
		17	TS	No Abnormality Detected
		18	TS	No Abnormality Detected
III	250	25	TS	No Abnormality Detected
		26	TS	No Abnormality Detected
		27	TS	No Abnormality Detected
		28	TS	No Abnormality Detected
		29	TS	No Abnormality Detected
		30	TS	No Abnormality Detected
IV	500	37	TS	No Abnormality Detected
		38	TS	No Abnormality Detected
		39	TS	No Abnormality Detected
		40	TS	No Abnormality Detected
		41	TS	No Abnormality Detected
		42	TS	No Abnormality Detected
V	1000	49	TS	No Abnormality Detected
		50	TS	No Abnormality Detected
		51	TS	No Abnormality Detected
		52	TS	No Abnormality Detected
		53	TS	No Abnormality Detected
		54	TS	No Abnormality Detected

TS = Terminal Sacrifice

APPENDIX NO.V (Contd.)

INDIVIDUAL ANIMAL - GROSS PATHOLOGY FINDINGS

Dose Range Finder: Study Number 17781
Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Day on Test : 29

Group Number	Dose mg/kg	Animal Number	Animal Fate	Gross pathology findings
I	0	7	TS	No Abnormality Detected
		8	TS	No Abnormality Detected
		9	TS	No Abnormality Detected
		10	TS	No Abnormality Detected
		11	TS	No Abnormality Detected
		12	TS	No Abnormality Detected
II	100	19	TS	No Abnormality Detected
		20	TS	No Abnormality Detected
		21	TS	No Abnormality Detected
		22	TS	No Abnormality Detected
		23	TS	No Abnormality Detected
		24	TS	No Abnormality Detected
III	250	31	TS	No Abnormality Detected
		32	TS	No Abnormality Detected
		33	TS	No Abnormality Detected
		34	TS	No Abnormality Detected
		35	TS	No Abnormality Detected
		36	TS	No Abnormality Detected
IV	500	43	TS	No Abnormality Detected
		44	TS	No Abnormality Detected
		45	TS	No Abnormality Detected
		46	TS	No Abnormality Detected
		47	TS	No Abnormality Detected
		48	TS	No Abnormality Detected
V	1000	55	TS	No Abnormality Detected
		56	TS	No Abnormality Detected
		57	TS	No Abnormality Detected
		58	TS	No Abnormality Detected
		59	TS	No Abnormality Detected
		60	TS	No Abnormality Detected

TS = Terminal Sacrifice

SECTION II

MAIN STUDY (90 DAY)

FIGURES, TABLES AND APPENDICES

FIG NO.V - MALE
GROUP MEAN BODY WEIGHT (g)

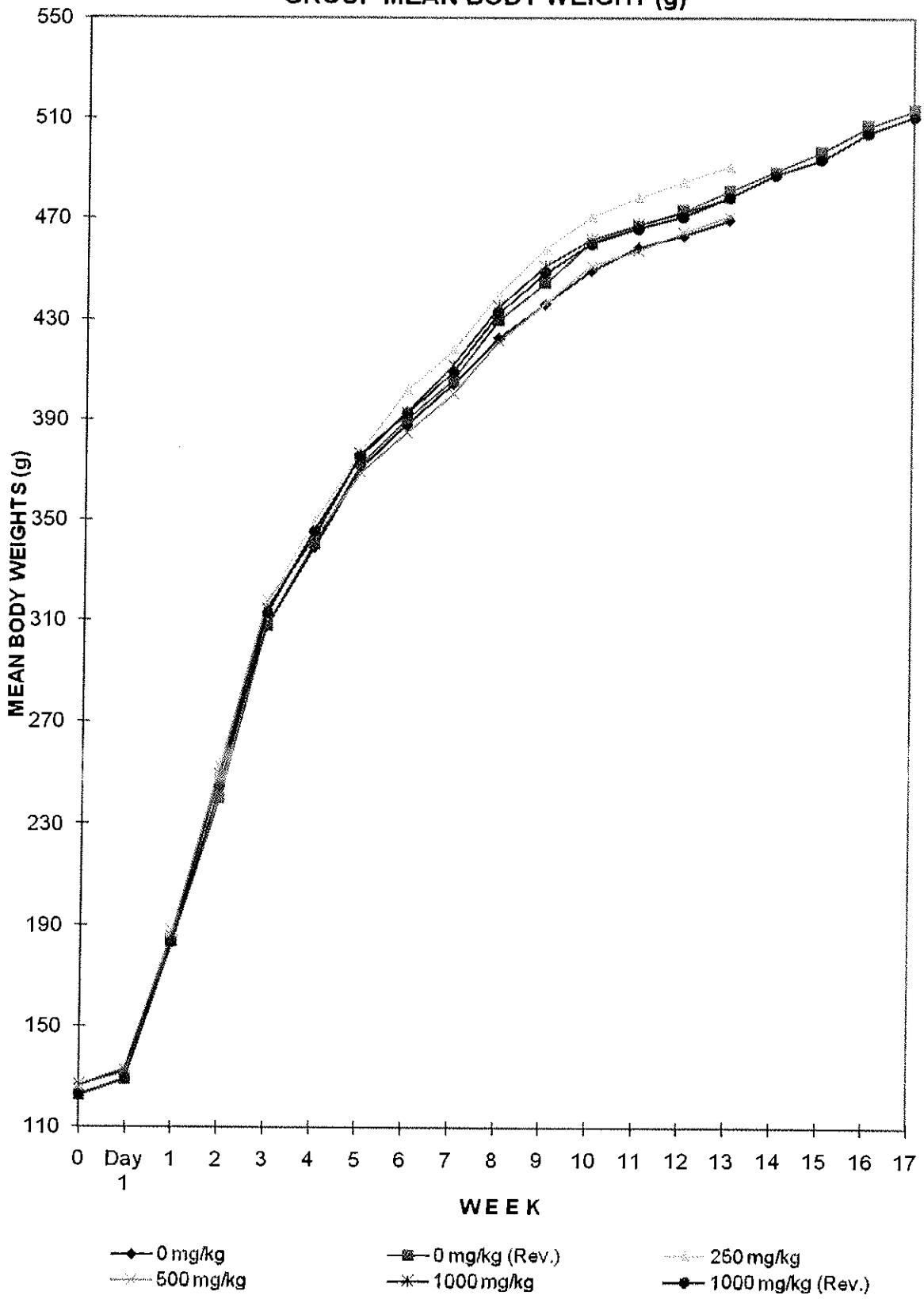

FIG NO.VI - FEMALE
GROUP MEAN BODY WEIGHT (g)

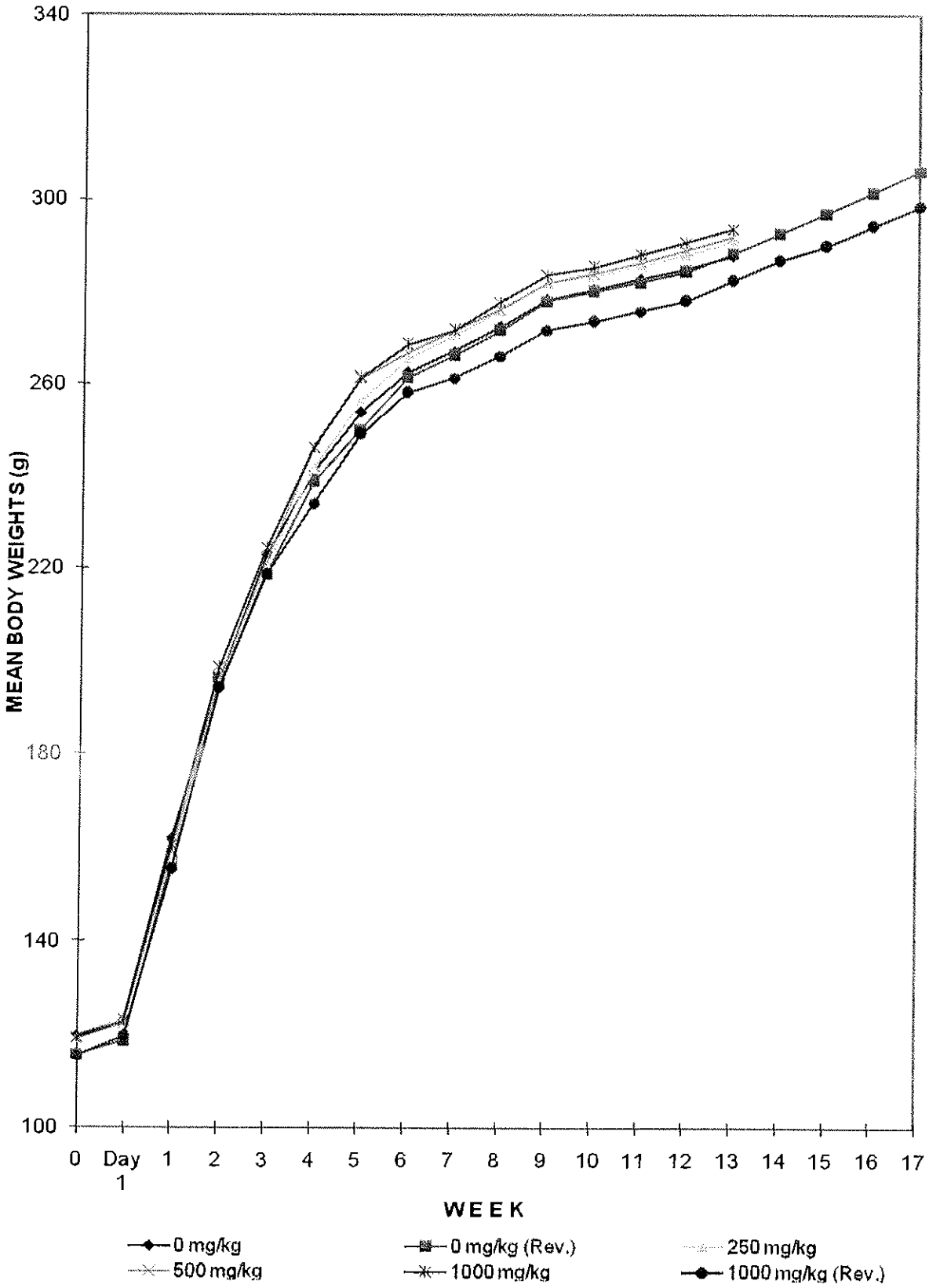

FIG NO.VII - MALE
GROUP MEAN FEED CONSUMPTION (g/animal)

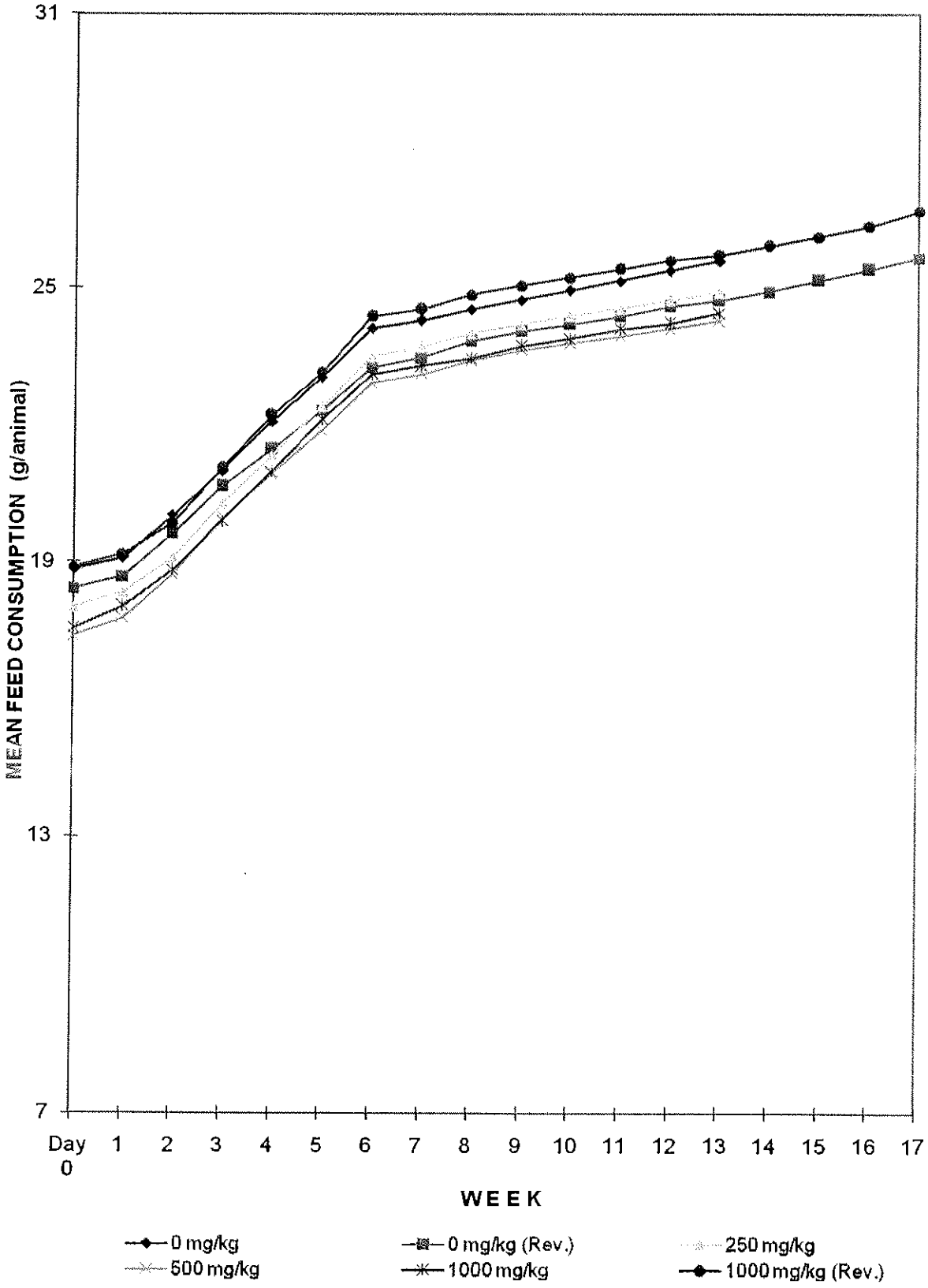

FIG NO.VIII - FEMALE
GROUP MEAN FEED CONSUMPTION (g/animal)

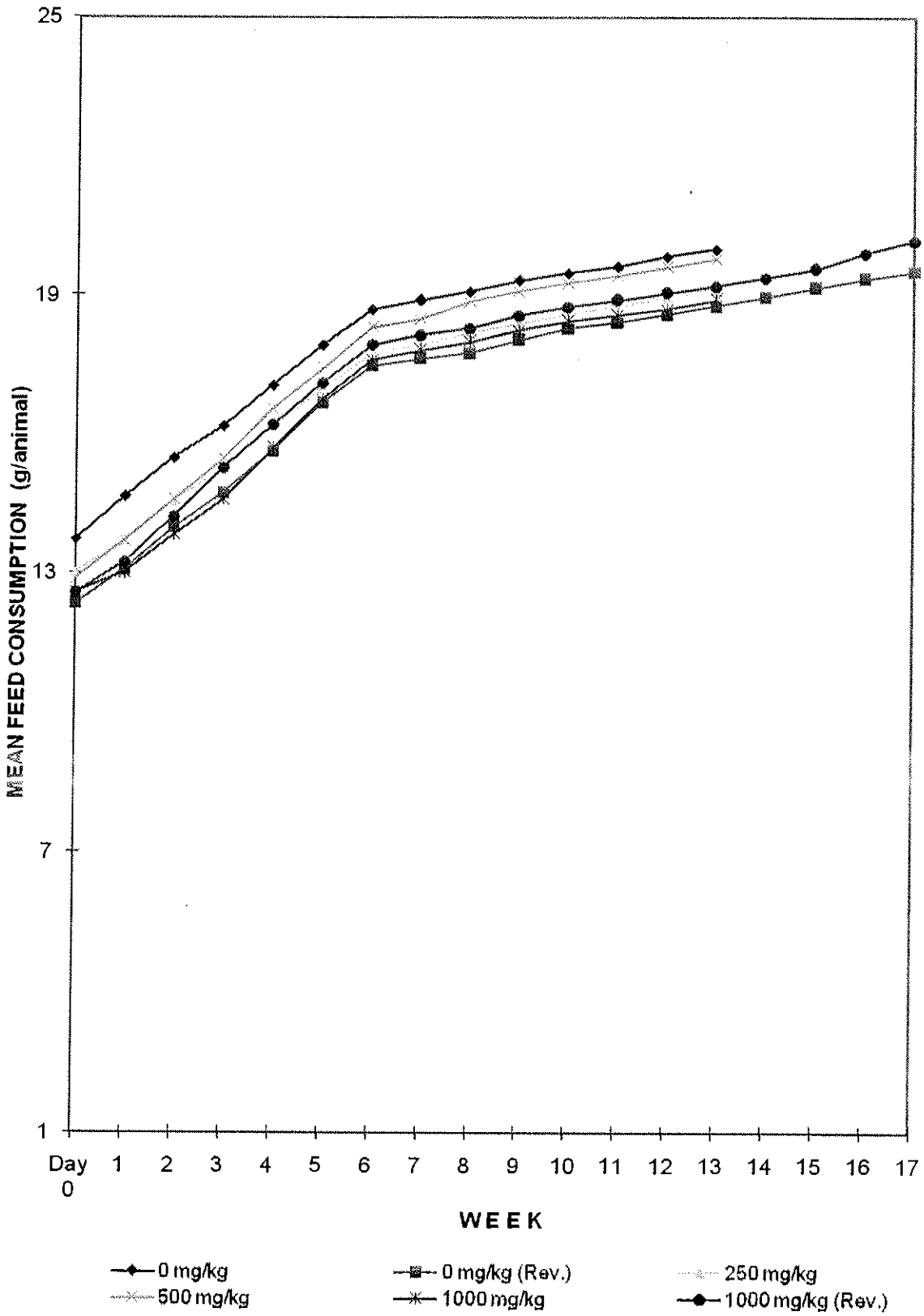

TABLE NO.I

ALLOCATION OF ANIMALS TO VARIOUS GROUPS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Group Number	Dose (mg/kg)	Sex	Animal Numbers
I	0	Male	1 - 10
		Female	11 - 20
II	0 (Rev.)	Male	21 - 26
		Female	27 - 32
III	250	Male	33 - 42
		Female	43 - 52
IV	500	Male	53 - 62
		Female	63 - 72
V	1000	Male	73 - 82
		Female	83 - 92
VI	1000 (Rev.)	Male	93 - 98
		Female	99 - 104

Rev. = Reversal

TABLE NO.J

VIABILITY

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Under the conditions of the present study, the following mortality rates were recorded:

Group Number	Dose (mg/kg body weight)		Mortality			
			Males		Females	
	Male	Female	Absolute	Relative %	Absolute	Relative %
I	0	0	0/10	0	0/10	0
II	0 (Rev.)	0 (Rev.)	0/6	0	0/6	0
III	250	250	0/10	0	0/10	0
IV	500	500	0/10	0	0/10	0
V	1000	1000	0/10	0	0/10	0
VI	1000 (Rev.)	1000 (Rev.)	0/6	0	0/6	0

Rev. = Reversal

TABLE NO.K

GROUP MEAN BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number	Dose mg/kg		WEEKS							
			0	Day 1	1	2	3	4	5	6
I	0	Mean	126.78	132.05	185.38	249.80	307.91	339.13	371.19	387.98
		± SD	9.95	9.57	11.33	5.39	14.98	16.15	16.52	19.43
II	0 (Rev.)	Mean	122.67	129.10	183.83	240.57	308.23	340.35	372.57	390.33
		± SD	11.59	11.59	7.64	12.14	6.67	10.37	9.40	10.21
III	250	Mean	127.06	133.95	188.06	254.34	317.27	349.51	377.64	401.92
		± SD	10.53	10.64	10.45	18.54	19.64	23.69	23.84	28.21
IV	500	Mean	126.51	133.20	187.80	252.76	317.62	342.67	369.05	384.79
		± SD	10.08	9.90	8.07	12.51	17.26	19.59	23.52	25.25
V	1000	Mean	126.60	132.94	185.52	249.74	314.61	343.36	376.75	392.95
		± SD	9.80	9.49	15.33	14.73	18.37	21.40	30.14	34.86
VI	1000 (Rev.)	Mean	123.07	129.30	183.55	244.70	312.82	345.65	375.85	392.72
		± SD	11.10	10.88	9.45	13.85	10.73	10.36	22.07	25.07

Group Number	Dose mg/kg		WEEKS						
			7	8	9	10	11	12	13
I	0	Mean	404.40	422.67	436.32	449.43	458.79	463.50	469.64
		± SD	24.39	30.40	28.18	25.49	25.63	25.33	25.15
II	0 (Rev.)	Mean	405.83	429.97	444.63	460.65	467.48	473.32	481.43
		± SD	11.50	8.84	8.76	9.35	11.48	12.35	12.60
III	250	Mean	417.76	440.36	458.18	470.90	478.57	484.72	490.76
		± SD	32.81	38.84	30.95	30.39	30.38	29.31	29.89
IV	500	Mean	400.43	421.44	436.66	451.24	457.36	464.93	471.09
		± SD	29.78	25.93	25.80	23.83	25.57	25.70	26.03
V	1000	Mean	411.78	435.46	451.62	462.09	467.58	472.88	478.45
		± SD	33.62	27.79	27.21	26.80	26.41	26.37	25.88
VI	1000 (Rev.)	Mean	409.28	432.93	448.63	460.17	466.17	471.02	478.67
		± SD	28.49	27.77	27.55	27.59	26.89	26.44	25.51

Group Number	Dose mg/kg		WEEKS			
			14	15	16	17
I	0	Mean				
		± SD				
II	0 (Rev.)	Mean	488.78	497.18	507.10	513.60
		± SD	12.53	12.16	12.64	11.91
III	250	Mean				
		± SD				
IV	500	Mean				
		± SD				
V	1000	Mean				
		± SD				
VI	1000 (Rev.)	Mean	487.65	493.95	504.50	511.08
		± SD	25.04	24.97	24.56	24.29

Rev. = Reversal

TABLE NO.K (Contd.)

GROUP MEAN BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number	Dose mg/kg		WEEKS							
			0	Day 1	1	2	3	4	5	6
I	0	Mean	119.79	123.18	162.11	195.78	222.81	241.02	253.99	262.49
		± SD	9.27	9.30	10.70	12.77	13.31	13.44	13.81	13.58
II	0 (Rev.)	Mean	115.67	118.70	157.35	196.35	218.78	238.88	250.28	261.48
		± SD	10.20	10.15	6.42	6.89	9.49	6.36	5.94	6.20
III	250	Mean	119.34	123.25	158.02	194.54	220.66	241.78	256.34	265.47
		± SD	9.84	9.61	8.07	9.40	9.08	10.23	12.31	10.13
IV	500	Mean	119.18	122.43	159.41	195.91	221.68	246.36	261.25	266.76
		± SD	9.39	9.51	10.31	11.56	9.07	16.66	15.91	16.13
V	1000	Mean	119.36	122.95	160.52	198.72	224.40	246.37	261.45	268.59
		± SD	8.97	9.42	8.38	6.50	5.35	10.83	15.10	15.00
VI	1000 (Rev.)	Mean	115.48	119.67	155.50	194.42	218.73	234.28	249.30	258.20
		± SD	9.23	9.35	7.86	9.40	11.72	8.95	9.17	12.57

Group Number	Dose mg/kg		WEEKS						
			7	8	9	10	11	12	13
I	0	Mean	267.17	272.44	278.28	280.52	282.84	284.98	287.72
		± SD	12.58	12.14	12.56	12.80	12.53	12.89	13.54
II	0 (Rev.)	Mean	266.15	271.63	277.97	280.05	282.13	284.35	288.35
		± SD	8.08	7.80	8.05	8.04	8.31	8.22	8.13
III	250	Mean	270.54	275.85	281.90	283.31	285.52	288.03	290.75
		± SD	8.08	10.24	10.20	10.37	9.99	10.46	10.51
IV	500	Mean	271.61	276.24	282.05	283.81	286.37	289.10	291.92
		± SD	18.61	19.08	18.35	18.41	18.23	18.35	18.38
V	1000	Mean	271.56	277.83	283.61	285.28	288.12	290.84	293.63
		± SD	14.86	17.37	17.25	17.16	17.06	16.73	16.83
VI	1000 (Rev.)	Mean	261.30	266.05	271.67	273.58	275.87	278.08	282.47
		± SD	12.53	12.06	11.23	11.21	11.36	11.42	12.21

Group Number	Dose mg/kg		WEEKS			
			14	15	16	17
I	0	Mean				
		± SD				
II	0 (Rev.)	Mean	292.67	297.05	301.63	306.12
		± SD	7.87	7.34	7.46	7.69
III	250	Mean				
		± SD				
IV	500	Mean				
		± SD				
V	1000	Mean				
		± SD				
VI	1000 (Rev.)	Mean	286.75	290.03	294.40	298.48
		± SD	12.86	13.24	12.89	12.59

Rev. = Reversal

TABLE NO.L

GROUP MEAN FEED CONSUMPTION (g/animal)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number	Dose mg/kg		WEEKS						
			Day 0	1	2	3	4	5	6
I	0	Mean	18.85	19.09	20.02	21.00	22.08	23.05	24.10
II	0 (Rev.)	Mean	18.42	18.68	19.62	20.65	21.47	22.32	23.25
III	250	Mean	18.02	18.33	19.09	20.27	21.33	22.41	23.49
IV	500	Mean	17.38	17.77	18.73	19.95	20.93	21.88	22.91
V	1000	Mean	17.55	18.03	18.83	19.89	20.97	22.12	23.10
VI	1000 (Rev.)	Mean	18.88	19.17	19.85	21.05	22.22	23.15	24.38

Group Number	Dose mg/kg		WEEKS						
			7	8	9	10	11	12	13
I	0	Mean	24.29	24.54	24.74	24.95	25.16	25.38	25.60
II	0 (Rev.)	Mean	23.47	23.83	24.05	24.20	24.38	24.60	24.73
III	250	Mean	23.70	23.99	24.19	24.39	24.55	24.73	24.90
IV	500	Mean	23.10	23.40	23.63	23.77	23.94	24.11	24.28
V	1000	Mean	23.29	23.46	23.72	23.88	24.09	24.23	24.46
VI	1000 (Rev.)	Mean	24.53	24.85	25.05	25.23	25.42	25.60	25.73

Group Number	Dose mg/kg		WEEKS			
			14	15	16	17
I	0	Mean				
II	0 (Rev.)	Mean	24.92	25.17	25.42	25.67
III	250	Mean				
IV	500	Mean				
V	1000	Mean				
VI	1000 (Rev.)	Mean	25.92	26.13	26.37	26.70

Rev. = Reversal

TABLE NO.L (Contd.)

GROUP MEAN FEED CONSUMPTION (g/animal)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number	Dose mg/kg		WEEKS						
			Day 0	1	2	3	4	5	6
I	0	Mean	13.73	14.65	15.49	16.16	17.06	17.90	18.69
II	0 (Rev.)	Mean	12.35	13.08	13.98	14.73	15.63	16.68	17.47
III	250	Mean	13.01	13.69	14.55	15.24	16.17	16.98	17.73
IV	500	Mean	12.88	13.70	14.59	15.46	16.54	17.40	18.30
V	1000	Mean	12.58	13.01	13.83	14.59	15.68	16.74	17.59
VI	1000 (Rev.)	Mean	12.57	13.23	14.22	15.27	16.20	17.10	17.92

Group Number	Dose mg/kg		WEEKS						
			7	8	9	10	11	12	13
I	0	Mean	18.90	19.09	19.32	19.49	19.62	19.85	20.00
II	0 (Rev.)	Mean	17.62	17.75	18.03	18.28	18.42	18.60	18.78
III	250	Mean	17.91	18.17	18.37	18.60	18.75	18.95	19.13
IV	500	Mean	18.49	18.87	19.09	19.27	19.42	19.61	19.78
V	1000	Mean	17.80	17.98	18.24	18.45	18.59	18.71	18.90
VI	1000 (Rev.)	Mean	18.13	18.28	18.57	18.75	18.90	19.05	19.20

Group Number	Dose mg/kg		WEEKS			
			14	15	16	17
I	0	Mean				
II	0 (Rev.)	Mean	18.97	19.17	19.37	19.53
III	250	Mean				
IV	500	Mean				
V	1000	Mean				
VI	1000 (Rev.)	Mean	19.38	19.57	19.92	20.18

Rev. = Reversal

TABLE NO.M

OPHTHALMOSCOPIC EXAMINATION

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male
Day : 0

Group Number	Dose mg/kg	Ophthalmoscopic Finding	Total Number of Animals	Animal Number
I	0	No abnormality detected	10	1 - 10
II	0 (Rev.)	No abnormality detected	6	21 - 26
III	250	No abnormality detected	10	33 - 42
IV	500	No abnormality detected	10	53 - 62
V	1000	No abnormality detected	10	73 - 82
VI	1000 (Rev.)	No abnormality detected	6	93 - 98

Sex : Female
Day : 0

Group Number	Dose mg/kg	Ophthalmoscopic Finding	Total Number of Animals	Animal Number
I	0	No abnormality detected	10	11 - 20
II	0 (Rev.)	No abnormality detected	6	27 - 32
III	250	No abnormality detected	10	43 - 52
IV	500	No abnormality detected	10	63 - 72
V	1000	No abnormality detected	10	83 - 92
VI	1000 (Rev.)	No abnormality detected	6	99 - 104

Rev. = Reversal

TABLE NO.M (Contd.)

OPHTHALMOSCOPIC EXAMINATION

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male
Day : 90

Group Number	Dose mg/kg	Ophthalmoscopic Finding	Total Number of Animals	Animal Number
I	0	No abnormality detected	10	1 - 10
II	0 (Rev.)	No abnormality detected	6	21 - 26
III	250	No abnormality detected	10	33 - 42
IV	500	No abnormality detected	10	53 - 62
V	1000	No abnormality detected	10	73 - 82
VI	1000 (Rev.)	No abnormality detected	6	93 - 98

Sex : Female
Day : 90

Group Number	Dose mg/kg	Ophthalmoscopic Finding	Total Number of Animals	Animal Number
I	0	No abnormality detected	10	11 - 20
II	0 (Rev.)	No abnormality detected	6	27 - 32
III	250	No abnormality detected	10	43 - 52
IV	500	No abnormality detected	10	63 - 72
V	1000	No abnormality detected	10	83 - 92
VI	1000 (Rev.)	No abnormality detected	6	99 - 104

Rev. = Reversal

TABLE NO.N

SUMMARY OF CLINICAL OBSERVATIONS AND GENERAL APPEARANCE

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number	Dose mg/kg	Observed Signs	Total Number of Animals	Animal Number	Period of signs in days from - to
I	0	Nil	10	1 - 10	1 - 90
II	0 (Rev.)	Nil	6	21 - 26	1 - 118
III	250	Nil	10	33 - 42	1 - 90
IV	500	Nil	10	53 - 62	1 - 90
V	1000	Nil	10	73 - 82	1 - 90
VI	1000 (Rev.)	Nil	6	93 - 98	1 - 118

Rev. = Reversal

TABLE NO.N (Contd.)

SUMMARY OF CLINICAL OBSERVATIONS AND GENERAL APPEARANCE

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number	Dose mg/kg	Observed Signs	Total Number of Animals	Animal Number	Period of signs in days from - to
I	0	Nil	10	11 - 20	1 - 90
II	0 (Rev.)	Nil	6	27 - 32	1 - 118
III	250	Nil	10	43 - 52	1 - 90
IV	500	Nil	10	63 - 72	1 - 90
V	1000	Nil	10	83 - 92	1 - 90
VI	1000 (Rev.)	Nil	6	99 - 104	1 - 118

Rev. = Reversal

TABLE NO.O

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Time : Before dosing (Acclimation)

Group Number : Not Applicable

Dose : Not Applicable

Animal Number	1-15	16-30	31-45	46-59
Week	0	0	0	0
Number of animals observed	15	15	15	14
Number of animals within normal limit	15/15	15/15	15/15	14/14
Number of animals with significant deviation	0/15	0/15	0/15	0/14
Parameters				
Behavior in Home cage				
Awake	8/15	7/15	12/15	7/14
Engaged in apparently normal movement	7/15	8/15	3/15	7/14
Alterations Home cage : No alterations	15/15	15/15	15/15	14/14
Vocalizations : No vocalization	15/15	15/15	15/15	14/14
Respiration : Normal	15/15	15/15	15/15	14/14
Palpebral closer : Eyelids wide open	15/15	15/15	15/15	14/14
Reaction to removal				
Sits quietly and is easily removed	7/15	5/15	8/15	5/14
Vocalization without resistance	8/15	10/15	7/15	9/14
Reaction to handling				
Quiet with no resistance	6/15	7/15	9/15	8/14
Vocalization without resistance	9/15	8/15	6/15	6/14
Urination				
No urination during the observation	3/15	4/15	4/15	7/14
Urine present; quantity is not excessive	12/15	11/15	11/15	7/14
Defecation				
No defecation during the observation	4/15	4/15	7/15	5/14
Fecal boluses have normal consistency	11/15	11/15	8/15	9/14
Prominence of Eye : Normal	15/15	15/15	15/15	14/14
Lacrimation : No excess lacrimation	15/15	15/15	15/15	14/14
Salivation : No excess salivation	15/15	15/15	15/15	14/14
Piloerection : Absent	15/15	15/15	15/15	14/14
Examination of mucous membrane : Normal	15/15	15/15	15/15	14/14
Examination of skin/fur : Normal	15/15	15/15	15/15	14/14
Examination of natural orifices : Normal	15/15	15/15	15/15	14/14
Animal appearance : Clean and groomed	15/15	15/15	15/15	14/14
Stereotype behaviour : Absent	15/15	15/15	15/15	14/14
Bizzare behaviour : Absent	15/15	15/15	15/15	14/14
Rearing (No.) Mean	11.27	11.53	10.80	11.57
± S.D.	1.94	2.07	1.82	2.31
Clonic movements : None/Normal	15/15	15/15	15/15	14/14
Tonic movements : None/Normal	15/15	15/15	15/15	14/14
Gait pattern : Normal	15/15	15/15	15/15	14/14
Severity of gait (1-3)	-	-	-	-
Mobility score : Normal	15/15	15/15	15/15	14/14
Pupillary response : Response (Miosis)	15/15	15/15	15/15	14/14

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Time : Before dosing (Acclimation)

Group Number : Not Applicable

Dose : Not Applicable

Animal Number	66-80	81-95	96-110	111-124
Week	0	0	0	0
Number of animals observed	15	15	15	14
Number of animals within normal limit	15/15	15/15	15/15	14/14
Number of animals with significant deviation	0/15	0/15	0/15	0/14
Parameters				
Behavior in Home cage				
Awake	8/15	7/15	8/15	9/14
Engaged in apparently normal movement	7/15	8/15	7/15	5/14
Alterations Home cage : No alterations	15/15	15/15	15/15	14/14
Vocalizations : No vocalization	15/15	15/15	15/15	14/14
Respiration : Normal	15/15	15/15	15/15	14/14
Palpebral closer : Eyelids wide open	15/15	15/15	15/15	14/14
Reaction to removal				
Sits quietly and is easily removed	8/15	7/15	7/15	4/14
Vocalization without resistance	7/15	8/15	8/15	10/14
Reaction to handling				
Quiet with no resistance	10/15	8/15	9/15	9/14
Vocalization without resistance	5/15	7/15	6/15	5/14
Urination				
No urination during the observation	5/15	4/15	4/15	7/14
Urine present; quantity is not excessive	10/15	11/15	11/15	7/14
Defecation				
No defecation during the observation	5/15	3/15	6/15	4/14
Fecal boluses have normal consistency	10/15	12/15	9/15	10/14
Prominence of Eye : Normal	15/15	15/15	15/15	14/14
Lacrimation : No excess lacrimation	15/15	15/15	15/15	14/14
Salivation : No excess salivation	15/15	15/15	15/15	14/14
Piloerection : Absent	15/15	15/15	15/15	14/14
Examination of mucous membrane : Normal	15/15	15/15	15/15	14/14
Examination of skin/fur : Normal	15/15	15/15	15/15	14/14
Examination of natural orifices : Normal	15/15	15/15	15/15	14/14
Animal appearance : Clean and groomed	15/15	15/15	15/15	14/14
Stereotype behaviour : Absent	15/15	15/15	15/15	14/14
Bizzare behaviour : Absent	15/15	15/15	15/15	14/14
Rearing (No.) Mean	11.67	11.87	11.93	12.00
± S.D.	2.16	2.10	2.12	2.00
Clonic movements : None/Normal	15/15	15/15	15/15	14/14
Tonic movements : None/Normal	15/15	15/15	15/15	14/14
Gait pattern : Normal	15/15	15/15	15/15	14/14
Severity of gait (1-3)	-	-	-	-
Mobility score : Normal	15/15	15/15	15/15	14/14
Pupillary response : Response (Miosis)	15/15	15/15	15/15	14/14

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number : I Dose : 0 mg/kg

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	10	10	10	10	10	10	10	10	10	10	10	10	10
Number of animals within normal limit	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Number of animals with significant deviation	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Parameters													
Behavior in Home cage													
Awake	7/10	8/10	8/10	9/10	9/10	9/10	8/10	9/10	5/10	6/10	8/10	7/10	8/10
Engaged in apparently normal movement	3/10	2/10	2/10	1/10	1/10	1/10	2/10	1/10	5/10	4/10	2/10	3/10	2/10
Alterations Home cage : No alterations	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Vocalizations : No vocalization	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Respiration : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Palpebral closer : Eyelids wide open	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Reaction to removal													
Sits quietly and is easily removed	6/10	8/10	8/10	8/10	8/10	9/10	8/10	8/10	5/10	8/10	8/10	7/10	8/10
Vocalization without resistance	4/10	2/10	2/10	2/10	2/10	1/10	2/10	2/10	5/10	2/10	2/10	3/10	2/10
Reaction to handling													
Quiet with no resistance	5/10	8/10	8/10	8/10	9/10	9/10	9/10	9/10	6/10	7/10	9/10	7/10	8/10
Vocalization without resistance	5/10	2/10	2/10	2/10	1/10	1/10	1/10	1/10	4/10	3/10	1/10	3/10	2/10
Urination													
No urination during the observation	4/10	5/10	7/10	7/10	7/10	7/10	7/10	7/10	2/10	6/10	7/10	6/10	7/10
Urine present; quantity is not excessive	6/10	5/10	3/10	3/10	3/10	3/10	3/10	3/10	8/10	4/10	3/10	4/10	3/10
Defecation													
No defecation during the observation	3/10	5/10	6/10	7/10	7/10	8/10	7/10	7/10	4/10	6/10	8/10	7/10	7/10
Fecal boluses have normal consistency	7/10	5/10	4/10	3/10	3/10	2/10	3/10	3/10	6/10	4/10	2/10	3/10	3/10
Prominence of Eye : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Lacrimation : No excess lacrimation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Salivation : No excess salivation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Piloerection : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of mucous membrane : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of skin/fur : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of natural orifices : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Animal appearance : Clean and groomed	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Stereotype behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Bizzare behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Rearing (No.) Mean	11.20	12.30	13.70	14.60	15.60	16.30	13.00	12.10	12.10	11.60	11.60	10.40	10.80
± S.D.	1.99	1.83	2.06	1.90	1.51	1.49	2.00	1.52	1.45	1.26	0.97	1.58	1.23
Clonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Tonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Gait pattern : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Pupillary response : Response (Miosis)	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number : I Dose : 0 mg/kg

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	10	10	10	10	10	10	10	10	10	10	10	10	10
Number of animals within normal limit	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Number of animals with significant deviation	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Parameters													
Behavior in Home cage													
Awake	7/10	5/10	8/10	8/10	6/10	9/10	7/10	9/10	9/10	8/10	8/10	8/10	9/10
Engaged in apparently normal movement	3/10	5/10	2/10	2/10	4/10	1/10	3/10	1/10	1/10	2/10	2/10	2/10	1/10
Alterations Home cage : No alterations	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Vocalizations : No vocalization	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Respiration : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Palpebral closer : Eyelids wide open	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Reaction to removal													
Sits quictly and is easily removed	4/10	6/10	8/10	9/10	7/10	8/10	7/10	8/10	8/10	7/10	8/10	7/10	8/10
Vocalization without resistance	6/10	4/10	2/10	1/10	3/10	2/10	3/10	2/10	2/10	3/10	2/10	3/10	2/10
Reaction to handling													
Quiet with no resistance	7/10	7/10	8/10	8/10	7/10	8/10	7/10	8/10	9/10	7/10	9/10	7/10	8/10
Vocalization without resistance	3/10	3/10	2/10	2/10	3/10	2/10	3/10	2/10	1/10	3/10	1/10	3/10	2/10
Urination													
No urination during the observation	3/10	4/10	7/10	7/10	3/10	6/10	6/10	8/10	8/10	5/10	7/10	7/10	7/10
Urine present; quantity is not excessive	7/10	6/10	3/10	3/10	7/10	4/10	4/10	2/10	2/10	5/10	3/10	3/10	3/10
Defecation													
No defecation during the observation	2/10	3/10	6/10	7/10	4/10	8/10	7/10	8/10	8/10	6/10	7/10	6/10	6/10
Fecal boluses have normal consistency	8/10	7/10	4/10	3/10	6/10	2/10	3/10	2/10	2/10	4/10	3/10	4/10	4/10
Prominence of Eye : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Lacrimation : No excess lacrimation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Salivation : No excess salivation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Piloerection : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of mucous membrane : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of skin/fur : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of natural orifices : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Animal appearance : Clean and groomed	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Stereotype behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Bizzare behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Rearing (No.) Mean	12.20	13.20	14.40	15.40	16.30	17.40	14.70	14.00	13.00	13.40	11.90	11.60	11.50
± S.D.	2.30	1.03	1.17	1.43	1.70	1.65	2.31	1.83	1.94	1.58	1.66	2.17	1.35
Clonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Tonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Gait pattern : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Pupillary response : Response (Miosis)	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number : II

Dose : 0 mg/kg (Reversal)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	6	6	6	6	6	6	6	6	6	6	6	6	6
Number of animals within normal limit	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Number of animals with significant deviation	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Parameters													
Behavior in Home cage													
Awake	3/6	5/6	5/6	5/6	5/6	5/6	5/6	5/6	3/6	4/6	5/6	5/6	5/6
Engaged in apparently normal movement	3/6	1/6	1/6	1/6	1/6	1/6	1/6	1/6	3/6	2/6	1/6	1/6	1/6
Alterations Home cage : No alterations	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Vocalizations : No vocalization	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Respiration : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Palpebral closer : Eyelids wide open	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Reaction to removal													
Sits quietly and is easily removed	3/6	4/6	5/6	4/6	4/6	5/6	5/6	5/6	4/6	4/6	5/6	5/6	5/6
Vocalization without resistance	3/6	2/6	1/6	2/6	2/6	1/6	1/6	1/6	2/6	2/6	1/6	1/6	1/6
Reaction to handling													
Quiet with no resistance	4/6	4/6	5/6	5/6	4/6	5/6	5/6	5/6	3/6	4/6	4/6	4/6	5/6
Vocalization without resistance	2/6	2/6	1/6	1/6	2/6	1/6	1/6	1/6	3/6	2/6	2/6	2/6	1/6
Urination													
No urination during the observation	2/6	3/6	4/6	4/6	4/6	4/6	4/6	2/6	2/6	3/6	4/6	4/6	3/6
Urine present; quantity is not excessive	4/6	3/6	2/6	2/6	2/6	2/6	2/6	4/6	4/6	3/6	2/6	2/6	3/6
Defecation													
No defecation during the observation	2/6	4/6	3/6	4/6	3/6	4/6	5/6	3/6	2/6	4/6	4/6	4/6	4/6
Fecal boluses have normal consistency	4/6	2/6	3/6	2/6	3/6	2/6	1/6	3/6	4/6	2/6	2/6	2/6	2/6
Prominence of Eye : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Lacrimation : No excess lacrimation	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Salivation : No excess salivation	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Piloerection : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of mucous membrane : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of skin/fur : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of natural orifices : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Animal appearance : Clean and groomed	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Stereotype behaviour : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Bizzare behaviour : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Rearing (No.) Mean	11.00	12.67	13.83	14.67	15.83	16.50	14.83	12.83	13.17	12.50	12.17	10.67	10.50
± S.D.	2.83	2.16	2.23	1.97	2.14	2.26	1.94	1.47	1.60	1.87	1.17	1.21	1.05
Clonic movements : None/Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Tonic movements : None/Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Gait pattern : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Pupillary response : Response (Miosis)	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number : II

Dose : 0 mg/kg (Reversal)

Week	14	15	16	17
Number of animals observed	6	6	6	6
Number of animals within normal limit	6/6	6/6	6/6	6/6
Number of animals with significant deviation	0/6	0/6	0/6	0/6
Parameters				
Behavior in Home cage				
Awake	5/6	5/6	3/6	5/6
Engaged in apparently normal movement	1/6	1/6	3/6	1/6
Alterations Home cage : No alterations	6/6	6/6	6/6	6/6
Vocalizations : No vocalization	6/6	6/6	6/6	6/6
Respiration : Normal	6/6	6/6	6/6	6/6
Palpebral closer : Eyelids wide open	6/6	6/6	6/6	6/6
Reaction to removal				
Sits quietly and is easily removed	5/6	4/6	4/6	4/6
Vocalization without resistance	1/6	2/6	2/6	2/6
Reaction to handling				
Quiet with no resistance	5/6	4/6	4/6	4/6
Vocalization without resistance	1/6	2/6	2/6	2/6
Urination				
No urination during the observation	4/6	2/6	3/6	3/6
Urine present; quantity is not excessive	2/6	4/6	3/6	3/6
Defecation				
No defecation during the observation	4/6	4/6	2/6	4/6
Fecal boluses have normal consistency	2/6	2/6	4/6	2/6
Prominence of Eye : Normal	6/6	6/6	6/6	6/6
Lacrimation : No excess lacrimation	6/6	6/6	6/6	6/6
Salivation : No excess salivation	6/6	6/6	6/6	6/6
Piloerection : Absent	6/6	6/6	6/6	6/6
Examination of mucous membrane : Normal	6/6	6/6	6/6	6/6
Examination of skin/fur : Normal	6/6	6/6	6/6	6/6
Examination of natural orifices : Normal	6/6	6/6	6/6	6/6
Animal appearance : Clean and groomed	6/6	6/6	6/6	6/6
Stereotype behaviour : Absent	6/6	6/6	6/6	6/6
Bizzare behaviour : Absent	6/6	6/6	6/6	6/6
Rearing (No.) Mean	11.00	10.83	9.67	9.83
± S.D.	1.41	0.98	1.03	0.75
Clonic movements : None/Normal	6/6	6/6	6/6	6/6
Tonic movements : None/Normal	6/6	6/6	6/6	6/6
Gait pattern : Normal	6/6	6/6	6/6	6/6
Severity of gait (1-3)	-	-	-	-
Mobility score : Normal	6/6	6/6	6/6	6/6
Pupillary response : Response (Miosis)	6/6	6/6	6/6	6/6

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number : II

Dose : 0 mg/kg (Reversal)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	6	6	6	6	6	6	6	6	6	6	6	6	6
Number of animals within normal limit	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Number of animals with significant deviation	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Parameters													
Behavior in Home cage													
Awake	4/6	2/6	5/6	5/6	5/6	5/6	4/6	5/6	5/6	4/6	5/6	5/6	5/6
Engaged in apparently normal movement	2/6	4/6	1/6	1/6	1/6	1/6	2/6	1/6	1/6	2/6	1/6	1/6	1/6
Alterations Home cage : No alterations	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Vocalizations : No vocalization	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Respiration : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Palpebral closer : Eyelids wide open	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Reaction to removal													
Sits quietly and is easily removed	2/6	4/6	4/6	4/6	4/6	5/6	3/6	5/6	5/6	4/6	5/6	4/6	4/6
Vocalization without resistance	4/6	2/6	2/6	2/6	2/6	1/6	3/6	1/6	1/6	2/6	1/6	2/6	2/6
Reaction to handling													
Quiet with no resistance	4/6	3/6	5/6	5/6	5/6	5/6	4/6	5/6	5/6	4/6	4/6	5/6	4/6
Vocalization without resistance	2/6	3/6	1/6	1/6	1/6	1/6	2/6	1/6	1/6	2/6	2/6	1/6	2/6
Urination													
No urination during the observation	2/6	2/6	4/6	4/6	4/6	4/6	4/6	4/6	4/6	4/6	4/6	4/6	4/6
Urine present; quantity is not excessive	4/6	4/6	2/6	2/6	2/6	2/6	2/6	2/6	2/6	2/6	2/6	2/6	2/6
Defecation													
No defecation during the observation	3/6	2/6	4/6	3/6	4/6	4/6	4/6	4/6	5/6	3/6	4/6	3/6	4/6
Fecal boluses have normal consistency	3/6	4/6	2/6	3/6	2/6	2/6	2/6	2/6	1/6	3/6	2/6	3/6	2/6
Prominence of Eye : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Lacrimation : No excess lacrimation	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Salivation : No excess salivation	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Piloerection : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of mucous membrane : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of skin/fur : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of natural orifices : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Animal appearance : Clean and groomed	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Stereotype behaviour : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Bizzare behaviour : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Rearing (No.) Mean	11.67	13.33	14.83	16.17	17.00	18.17	14.83	14.00	15.00	15.83	13.17	11.50	12.17
± S.D.	2.16	1.21	1.17	1.60	1.67	1.83	2.32	1.41	1.41	1.17	1.72	1.22	1.17
Clonic movements : None/Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Tonic movements : None/Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Gait pattern : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Pupillary response : Response (Miosis)	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number : II

Dose : 0 mg/kg (Reversal)

Week	14	15	16	17
Number of animals observed	6	6	6	6
Number of animals within normal limit	6/6	6/6	6/6	6/6
Number of animals with significant deviation	0/6	0/6	0/6	0/6
Parameters				
Behavior in Home cage				
Awake	4/6	5/6	5/6	5/6
Engaged in apparently normal movement	2/6	1/6	1/6	1/6
Alterations Home cage : No alterations	6/6	6/6	6/6	6/6
Vocalizations : No vocalization	6/6	6/6	6/6	6/6
Respiration : Normal	6/6	6/6	6/6	6/6
Palpebral closer : Eyelids wide open	6/6	6/6	6/6	6/6
Reaction to removal				
Sits quietly and is easily removed	4/6	4/6	5/6	4/6
Vocalization without resistance	2/6	2/6	1/6	2/6
Reaction to handling				
Quiet with no resistance	5/6	4/6	4/6	5/6
Vocalization without resistance	1/6	2/6	2/6	1/6
Urination				
No urination during the observation	3/6	4/6	4/6	4/6
Urine present; quantity is not excessive	3/6	2/6	2/6	2/6
Defecation				
No defecation during the observation	3/6	4/6	4/6	4/6
Fecal boluses have normal consistency	3/6	2/6	2/6	2/6
Prominence of Eye : Normal	6/6	6/6	6/6	6/6
Lacrimation : No excess lacrimation	6/6	6/6	6/6	6/6
Salivation : No excess salivation	6/6	6/6	6/6	6/6
Piloerection : Absent	6/6	6/6	6/6	6/6
Examination of mucous membrane : Normal	6/6	6/6	6/6	6/6
Examination of skin/fur : Normal	6/6	6/6	6/6	6/6
Examination of natural orifices : Normal	6/6	6/6	6/6	6/6
Animal appearance : Clean and groomed	6/6	6/6	6/6	6/6
Stereotype behaviour : Absent	6/6	6/6	6/6	6/6
Bizzare behaviour : Absent	6/6	6/6	6/6	6/6
Rearing (No.) Mean	10.83	10.17	9.50	9.83
± S.D.	1.17	1.33	1.05	0.75
Clonic movements : None/Normal	6/6	6/6	6/6	6/6
Tonic movements : None/Normal	6/6	6/6	6/6	6/6
Gait pattern : Normal	6/6	6/6	6/6	6/6
Severity of gait (1-3)	-	-	-	-
Mobility score : Normal	6/6	6/6	6/6	6/6
Pupillary response : Response (Miosis)	6/6	6/6	6/6	6/6

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number : III Dose : 250 mg/kg

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	10	10	10	10	10	10	10	10	10	10	10	10	10
Number of animals within normal limit	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Number of animals with significant deviation	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Parameters													
Behavior in Home cage													
Awake	5/10	8/10	9/10	8/10	9/10	9/10	9/10	9/10	7/10	6/10	8/10	8/10	8/10
Engaged in apparently normal movement	5/10	2/10	1/10	2/10	1/10	1/10	1/10	1/10	3/10	4/10	2/10	2/10	2/10
Alterations Home cage : No alterations	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Vocalizations : No vocalization	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Respiration : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Palpebral closer : Eyelids wide open	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Reaction to removal													
Sits quietly and is easily removed	5/10	7/10	8/10	8/10	8/10	9/10	8/10	8/10	7/10	7/10	8/10	8/10	8/10
Vocalization without resistance	5/10	3/10	2/10	2/10	2/10	1/10	2/10	2/10	3/10	3/10	2/10	2/10	2/10
Reaction to handling													
Quiet with no resistance	7/10	8/10	8/10	8/10	8/10	9/10	9/10	8/10	6/10	7/10	8/10	8/10	8/10
Vocalization without resistance	3/10	2/10	2/10	2/10	2/10	1/10	1/10	2/10	4/10	3/10	2/10	2/10	2/10
Urination													
No urination during the observation	3/10	4/10	6/10	7/10	6/10	8/10	8/10	7/10	3/10	5/10	7/10	6/10	6/10
Urine present; quantity is not excessive	7/10	6/10	4/10	3/10	4/10	2/10	2/10	3/10	7/10	5/10	3/10	4/10	4/10
Defecation													
No defecation during the observation	2/10	6/10	7/10	5/10	7/10	7/10	8/10	8/10	4/10	6/10	6/10	6/10	7/10
Fecal boluses have normal consistency	8/10	4/10	3/10	5/10	3/10	3/10	2/10	2/10	6/10	4/10	4/10	4/10	3/10
Prominence of Eye : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Lacrimation : No excess lacrimation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Salivation : No excess salivation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Piloerection : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of mucous membrane : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of skin/fur : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of natural orifices : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Animal appearance : Clean and groomed	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Stereotype behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Bizzare behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Rearing (No.) Mean	11.70	12.80	13.70	14.50	15.40	16.20	14.10	13.00	12.70	12.00	11.80	11.00	11.20
± S.D.	1.89	1.75	1.49	2.07	1.96	1.99	2.13	1.25	1.34	1.49	1.23	1.15	1.23
Clonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Tonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Gait pattern : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Pupillary response : Response (Miosis)	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number : III

Dose : 250 mg/kg

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	10	10	10	10	10	10	10	10	10	10	10	10	10
Number of animals within normal limit	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Number of animals with significant deviation	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Parameters													
Behavior in Home cage													
Awake	6/10	5/10	9/10	8/10	7/10	6/10	6/10	9/10	9/10	6/10	7/10	8/10	8/10
Engaged in apparently normal movement	4/10	5/10	1/10	2/10	3/10	4/10	4/10	1/10	1/10	4/10	3/10	2/10	2/10
Alterations Home cage : No alterations	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Vocalizations : No vocalization	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Respiration : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Palpebral closer : Eyelids wide open	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Reaction to removal													
Sits quietly and is easily removed	5/10	7/10	6/10	8/10	7/10	7/10	6/10	8/10	9/10	7/10	8/10	7/10	8/10
Vocalization without resistance	5/10	3/10	4/10	2/10	3/10	3/10	4/10	2/10	1/10	3/10	2/10	3/10	2/10
Reaction to handling													
Quiet with no resistance	7/10	7/10	8/10	8/10	8/10	7/10	8/10	9/10	8/10	6/10	8/10	7/10	8/10
Vocalization without resistance	3/10	3/10	2/10	2/10	2/10	3/10	2/10	1/10	2/10	4/10	2/10	3/10	2/10
Urination													
No urination during the observation	5/10	5/10	7/10	6/10	6/10	6/10	6/10	7/10	8/10	6/10	7/10	6/10	8/10
Urine present; quantity is not excessive	5/10	5/10	3/10	4/10	4/10	4/10	4/10	3/10	2/10	4/10	3/10	4/10	2/10
Defecation													
No defecation during the observation	5/10	3/10	7/10	8/10	7/10	6/10	6/10	7/10	8/10	6/10	7/10	7/10	7/10
Fecal boluses have normal consistency	5/10	7/10	3/10	2/10	3/10	4/10	4/10	3/10	2/10	4/10	3/10	3/10	3/10
Prominence of Eye : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Lacrimation : No excess lacrimation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Salivation : No excess salivation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Piloerection : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of mucous membrane : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of skin/fur : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of natural orifices : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Animal appearance : Clean and groomed	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Stereotype behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Bizzare behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Rearing (No.) Mean	12.60	13.80	14.90	16.10	17.10	17.00	14.60	13.60	12.70	13.20	12.00	11.10	11.30
± S.D.	2.22	1.55	1.79	1.73	1.37	1.94	2.41	1.71	1.42	1.62	1.25	1.91	1.64
Clonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Tonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Gait pattern : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Pupillary response : Response (Miosis)	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number : IV

Dose : 500 mg/kg

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	10	10	10	10	10	10	10	10	10	10	10	10	10
Number of animals within normal limit	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Number of animals with significant deviation	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Parameters													
Behavior in Home cage													
Awake	6/10	5/10	8/10	8/10	4/10	7/10	5/10	8/10	7/10	8/10	8/10	8/10	8/10
Engaged in apparently normal movement	4/10	5/10	2/10	2/10	6/10	3/10	5/10	2/10	3/10	2/10	2/10	2/10	2/10
Alterations Home cage : No alterations	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Vocalizations : No vocalization	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Respiration : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Palpebral closer : Eyelids wide open	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Reaction to removal													
Sits quietly and is easily removed	5/10	5/10	8/10	8/10	6/10	8/10	6/10	7/10	6/10	8/10	8/10	7/10	8/10
Vocalization without resistance	5/10	5/10	2/10	2/10	4/10	2/10	4/10	3/10	4/10	2/10	2/10	3/10	2/10
Reaction to handling													
Quiet with no resistance	6/10	8/10	9/10	9/10	7/10	8/10	8/10	8/10	7/10	8/10	8/10	8/10	8/10
Vocalization without resistance	4/10	2/10	1/10	1/10	3/10	2/10	2/10	2/10	3/10	2/10	2/10	2/10	2/10
Urination													
No urination during the observation	4/10	4/10	7/10	7/10	2/10	3/10	2/10	7/10	5/10	7/10	7/10	7/10	6/10
Urine present; quantity is not excessive	6/10	6/10	3/10	3/10	8/10	7/10	8/10	3/10	5/10	3/10	3/10	3/10	4/10
Defecation													
No defecation during the observation	4/10	3/10	7/10	7/10	3/10	7/10	3/10	8/10	6/10	7/10	8/10	6/10	7/10
Fecal boluses have normal consistency	6/10	7/10	3/10	3/10	7/10	3/10	7/10	2/10	4/10	3/10	2/10	4/10	3/10
Prominence of Eye : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Lacrimation : No excess lacrimation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Salivation : No excess salivation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Piloerection : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of mucous membrane : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of skin/fur : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of natural orifices : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Animal appearance : Clean and groomed	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Stereotype behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Bizzare behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Rearing (No.) Mean	11.70	12.90	13.70	14.60	16.10	16.70	12.10	12.70	12.20	12.00	11.70	11.60	11.70
± S.D.	1.89	1.91	1.64	1.90	1.45	1.34	1.66	1.49	1.14	1.15	1.25	1.84	1.34
Clonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Tonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Gait pattern : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Pupillary response : Response (Miosis)	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number : IV

Dose : 500 mg/kg

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	10	10	10	10	10	10	10	10	10	10	10	10	10
Number of animals within normal limit	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Number of animals with significant deviation	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Parameters													
Behavior in Home cage													
Awake	5/10	7/10	8/10	9/10	8/10	8/10	9/10	9/10	9/10	5/10	8/10	7/10	9/10
Engaged in apparently normal movement	5/10	3/10	2/10	1/10	2/10	2/10	1/10	1/10	1/10	5/10	2/10	3/10	1/10
Alterations Home cage : No alterations	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Vocalizations : No vocalization	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Respiration : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Palpebral closer : Eyelids wide open	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Reaction to removal													
Sits quietly and is easily removed	4/10	6/10	7/10	8/10	8/10	7/10	8/10	8/10	8/10	7/10	8/10	8/10	8/10
Vocalization without resistance	6/10	4/10	3/10	2/10	2/10	3/10	2/10	2/10	2/10	3/10	2/10	2/10	2/10
Reaction to handling													
Quiet with no resistance	6/10	7/10	8/10	8/10	8/10	7/10	9/10	9/10	7/10	8/10	8/10	7/10	9/10
Vocalization without resistance	4/10	3/10	2/10	2/10	2/10	3/10	1/10	1/10	3/10	2/10	2/10	3/10	1/10
Urination													
No urination during the observation	4/10	6/10	7/10	8/10	7/10	7/10	8/10	8/10	6/10	6/10	7/10	6/10	6/10
Urine present; quantity is not excessive	6/10	4/10	3/10	2/10	3/10	3/10	2/10	2/10	4/10	4/10	3/10	4/10	4/10
Defecation													
No defecation during the observation	4/10	4/10	7/10	8/10	8/10	7/10	7/10	8/10	7/10	4/10	5/10	6/10	7/10
Fecal boluses have normal consistency	6/10	6/10	3/10	2/10	2/10	3/10	3/10	2/10	3/10	6/10	5/10	4/10	3/10
Prominence of Eye : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Lacrimation : No excess lacrimation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Salivation : No excess salivation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Piloerection : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of mucous membrane : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of skin/fur : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of natural orifices : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Animal appearance : Clean and groomed	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Stereotype behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Bizzare behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Rearing (No.) Mean	12.10	13.30	14.40	15.50	16.30	15.30	12.40	15.30	13.90	15.20	12.80	12.00	11.30
± S.D.	2.13	1.89	1.84	1.84	1.89	1.77	1.65	1.95	1.85	2.39	1.14	1.63	1.16
Clonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Tonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Gait pattern : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Pupillary response : Response (Miosis)	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number : V

Dose : 1000 mg/kg

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	10	10	10	10	10	10	10	10	10	10	10	10	10
Number of animals within normal limit	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Number of animals with significant deviation	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Parameters													
Behavior in Home cage													
Awake	5/10	5/10	9/10	8/10	5/10	8/10	5/10	9/10	6/10	8/10	9/10	8/10	9/10
Engaged in apparently normal movement	5/10	5/10	1/10	2/10	5/10	2/10	5/10	1/10	4/10	2/10	1/10	2/10	1/10
Alterations Home cage : No alterations	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Vocalizations : No vocalization	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Respiration : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Palpebral closer : Eyelids wide open	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Reaction to removal													
Sits quietly and is easily removed	6/10	7/10	8/10	8/10	6/10	6/10	6/10	8/10	7/10	8/10	8/10	7/10	8/10
Vocalization without resistance	4/10	3/10	2/10	2/10	4/10	4/10	4/10	2/10	3/10	2/10	2/10	3/10	2/10
Reaction to handling													
Quiet with no resistance	5/10	5/10	8/10	9/10	8/10	8/10	6/10	9/10	7/10	8/10	8/10	8/10	8/10
Vocalization without resistance	5/10	5/10	2/10	1/10	2/10	2/10	4/10	1/10	3/10	2/10	2/10	2/10	2/10
Urination													
No urination during the observation	3/10	4/10	7/10	8/10	2/10	6/10	2/10	7/10	5/10	7/10	8/10	7/10	7/10
Urine present; quantity is not excessive	7/10	6/10	3/10	2/10	8/10	4/10	8/10	3/10	5/10	3/10	2/10	3/10	3/10
Defecation													
No defecation during the observation	4/10	4/10	8/10	8/10	3/10	8/10	3/10	7/10	4/10	8/10	7/10	7/10	7/10
Fecal boluses have normal consistency	6/10	6/10	2/10	2/10	7/10	2/10	7/10	3/10	6/10	2/10	3/10	3/10	3/10
Prominence of Eye : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Lacrimation : No excess lacrimation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Salivation : No excess salivation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Piloerection : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of mucous membrane : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of skin/fur : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of natural orifices : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Animal appearance : Clean and groomed	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Stereotype behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Bizzare behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Rearing (No.) Mean	12.40	13.60	14.40	15.20	16.00	17.00	12.70	12.20	11.90	11.90	12.10	11.10	11.20
± S.D.	2.32	1.90	1.71	1.69	1.49	1.49	1.49	1.32	0.88	1.20	0.99	0.99	1.03
Clonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Tonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Gait pattern : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Pupillary response : Response (Miosis)	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number : V Dose : 1000 mg/kg

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	10	10	10	10	10	10	10	10	10	10	10	10	10
Number of animals within normal limit	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Number of animals with significant deviation	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Parameters													
Behavior in Home cage													
Awake	6/10	7/10	9/10	9/10	5/10	7/10	9/10	9/10	9/10	6/10	8/10	7/10	9/10
Engaged in apparently normal movement	4/10	3/10	1/10	1/10	5/10	3/10	1/10	1/10	1/10	4/10	2/10	3/10	1/10
Alterations Home cage : No alterations	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Vocalizations : No vocalization	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Respiration : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Palpebral closer : Eyelids wide open	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Reaction to removal													
Sits quietly and is easily removed	4/10	6/10	7/10	8/10	7/10	7/10	8/10	8/10	9/10	6/10	8/10	7/10	8/10
Vocalization without resistance	6/10	4/10	3/10	2/10	3/10	3/10	2/10	2/10	1/10	4/10	2/10	3/10	2/10
Reaction to handling													
Quiet with no resistance	7/10	7/10	8/10	8/10	6/10	6/10	8/10	9/10	9/10	7/10	8/10	8/10	8/10
Vocalization without resistance	3/10	3/10	2/10	2/10	4/10	4/10	2/10	1/10	1/10	3/10	2/10	2/10	2/10
Urination													
No urination during the observation	4/10	3/10	7/10	8/10	3/10	7/10	8/10	8/10	7/10	6/10	7/10	7/10	7/10
Urine present; quantity is not excessive	6/10	7/10	3/10	2/10	7/10	3/10	2/10	2/10	3/10	4/10	3/10	3/10	3/10
Defecation													
No defecation during the observation	3/10	3/10	7/10	8/10	3/10	7/10	8/10	8/10	7/10	3/10	7/10	6/10	8/10
Fecal boluses have normal consistency	7/10	7/10	3/10	2/10	7/10	3/10	2/10	2/10	3/10	7/10	3/10	4/10	2/10
Prominence of Eye : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Lacrimation : No excess lacrimation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Salivation : No excess salivation	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Piloerection : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of mucous membrane : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of skin/fur : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Examination of natural orifices : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Animal appearance : Clean and groomed	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Stereotype behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Bizzare behaviour : Absent	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Rearing (No.) Mean	12.30	13.90	15.30	15.90	15.00	15.80	15.80	15.70	14.30	14.80	14.00	12.70	12.20
± S.D.	2.45	2.02	1.89	1.91	1.83	1.69	1.62	2.00	1.89	2.49	2.11	1.77	1.55
Clonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Tonic movements : None/Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Gait pattern : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10
Pupillary response : Response (Miosis)	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number : VI

Dose : 1000 mg/kg (Reversal)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	6	6	6	6	6	6	6	6	6	6	6	6	6
Number of animals within normal limit	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Number of animals with significant deviation	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Parameters													
Behavior in Home cage													
Awake	3/6	4/6	5/6	5/6	3/6	5/6	4/6	5/6	3/6	5/6	5/6	5/6	5/6
Engaged in apparently normal movement	3/6	2/6	1/6	1/6	3/6	1/6	2/6	1/6	3/6	1/6	1/6	1/6	1/6
Alterations Home cage : No alterations	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Vocalizations : No vocalization	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Respiration : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Palpebral closer : Eyelids wide open	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Reaction to removal													
Sits quietly and is easily removed	3/6	4/6	5/6	5/6	4/6	4/6	4/6	4/6	4/6	5/6	5/6	5/6	5/6
Vocalization without resistance	3/6	2/6	1/6	1/6	2/6	2/6	2/6	2/6	2/6	1/6	1/6	1/6	1/6
Reaction to handling													
Quiet with no resistance	3/6	3/6	5/6	5/6	4/6	5/6	4/6	5/6	4/6	5/6	5/6	5/6	5/6
Vocalization without resistance	3/6	3/6	1/6	1/6	2/6	1/6	2/6	1/6	2/6	1/6	1/6	1/6	1/6
Urination													
No urination during the observation	2/6	2/6	4/6	4/6	2/6	4/6	2/6	3/6	4/6	2/6	3/6	4/6	4/6
Urine present; quantity is not excessive	4/6	4/6	2/6	2/6	4/6	2/6	4/6	3/6	2/6	4/6	3/6	2/6	2/6
Defecation													
No defecation during the observation	3/6	2/6	4/6	4/6	3/6	3/6	2/6	3/6	3/6	2/6	4/6	4/6	4/6
Fecal boluses have normal consistency	3/6	4/6	2/6	2/6	3/6	3/6	4/6	3/6	3/6	4/6	2/6	2/6	2/6
Prominence of Eye : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Lacrimation : No excess lacrimation	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Salivation : No excess salivation	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Piloerection : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of mucous membrane : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of skin/fur : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of natural orifices : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Animal appearance : Clean and groomed	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Stereotype behaviour : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Bizzare behaviour : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Rearing (No.) Mean	11.67	13.30	13.83	15.50	15.00	16.50	13.50	12.17	12.00	12.67	12.50	10.83	11.17
± S.D.	2.16	1.63	1.47	1.64	1.67	1.64	1.38	1.17	1.10	1.03	1.05	0.98	1.17
Clonic movements : None/Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Tonic movements : None/Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Gait pattern : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Pupillary response : Response (Miosis)	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number : VI

Dose : 1000 mg/kg (Reversal)

Week	14	15	16	17
Number of animals observed	6	6	6	6
Number of animals within normal limit	6/6	6/6	6/6	6/6
Number of animals with significant deviation	0/6	0/6	0/6	0/6
Parameters				
Behavior in Home cage				
Awake	5/6	5/6	4/6	4/6
Engaged in apparently normal movement	1/6	1/6	2/6	2/6
Alterations Home cage : No alterations	6/6	6/6	6/6	6/6
Vocalizations : No vocalization	6/6	6/6	6/6	6/6
Respiration : Normal	6/6	6/6	6/6	6/6
Palpebral closer : Eyelids wide open	6/6	6/6	6/6	6/6
Reaction to removal				
Sits quietly and is easily removed	5/6	4/6	4/6	5/6
Vocalization without resistance	1/6	2/6	2/6	1/6
Reaction to handling				
Quiet with no resistance	5/6	4/6	4/6	4/6
Vocalization without resistance	1/6	2/6	2/6	2/6
Urination				
No urination during the observation	3/6	4/6	3/6	3/6
Urine present; quantity is not excessive	3/6	2/6	3/6	3/6
Defecation				
No defecation during the observation	5/6	3/6	3/6	4/6
Fecal boluses have normal consistency	1/6	3/6	3/6	2/6
Prominence of Eye : Normal	6/6	6/6	6/6	6/6
Lacrimation : No excess lacrimation	6/6	6/6	6/6	6/6
Salivation : No excess salivation	6/6	6/6	6/6	6/6
Piloerection : Absent	6/6	6/6	6/6	6/6
Examination of mucous membrane : Normal	6/6	6/6	6/6	6/6
Examination of skin/fur : Normal	6/6	6/6	6/6	6/6
Examination of natural orifices : Normal	6/6	6/6	6/6	6/6
Animal appearance : Clean and groomed	6/6	6/6	6/6	6/6
Stereotype behaviour : Absent	6/6	6/6	6/6	6/6
Bizzare behaviour : Absent	6/6	6/6	6/6	6/6
Rearing (No.) Mean	10.83	10.50	9.66	10.33
± S.D.	1.47	1.05	1.37	0.82
Clonic movements : None/Normal	6/6	6/6	6/6	6/6
Tonic movements : None/Normal	6/6	6/6	6/6	6/6
Gait pattern : Normal	6/6	6/6	6/6	6/6
Severity of gait (1-3)	-	-	-	-
Mobility score : Normal	6/6	6/6	6/6	6/6
Pupillary response : Response (Miosis)	6/6	6/6	6/6	6/6

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number : VI

Dose : 1000 mg/kg (Reversal)

Week	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of animals observed	6	6	6	6	6	6	6	6	6	6	6	6	6
Number of animals within normal limit	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Number of animals with significant deviation	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
Parameters													
Behavior in Home cage													
Awake	4/6	4/6	4/6	5/6	3/6	3/6	5/6	5/6	5/6	4/6	5/6	4/6	5/6
Engaged in apparently normal movement	2/6	2/6	2/6	1/6	3/6	3/6	1/6	1/6	1/6	2/6	1/6	2/6	1/6
Alterations Home cage : No alterations	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Vocalizations : No vocalization	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Respiration : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Palpebral closer : Eyelids wide open	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Reaction to removal													
Sits quietly and is easily removed	3/6	3/6	3/6	5/6	4/6	4/6	5/6	5/6	5/6	4/6	4/6	4/6	5/6
Vocalization without resistance	3/6	3/6	3/6	1/6	2/6	2/6	1/6	1/6	1/6	2/6	2/6	2/6	1/6
Reaction to handling													
Quiet with no resistance	3/6	3/6	5/6	4/6	4/6	4/6	5/6	5/6	5/6	4/6	5/6	5/6	4/6
Vocalization without resistance	3/6	3/6	1/6	2/6	2/6	2/6	1/6	1/6	1/6	2/6	1/6	1/6	2/6
Urination													
No urination during the observation	2/6	3/6	4/6	5/6	2/6	3/6	3/6	4/6	2/6	3/6	4/6	4/6	4/6
Urine present; quantity is not excessive	4/6	3/6	2/6	1/6	4/6	3/6	3/6	2/6	4/6	3/6	2/6	2/6	2/6
Defecation													
No defecation during the observation	2/6	2/6	4/6	5/6	3/6	4/6	3/6	4/6	2/6	3/6	4/6	2/6	4/6
Fecal boluses have normal consistency	4/6	4/6	2/6	1/6	3/6	2/6	3/6	2/6	4/6	3/6	2/6	4/6	2/6
Prominence of Eye : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Lacrimation : No excess lacrimation	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Salivation : No excess salivation	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Piloerection : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of mucous membrane : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of skin/fur : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Examination of natural orifices : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Animal appearance : Clean and groomed	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Stereotype behaviour : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Bizzare behaviour : Absent	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Rearing (No.) Mean	13.33	14.33	15.00	15.50	14.50	15.33	15.50	15.17	14.67	14.50	12.33	11.17	11.33
± S.D.	2.16	1.63	2.10	1.52	1.87	1.75	1.05	2.32	2.58	1.87	1.03	1.33	1.21
Clonic movements : None/Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Tonic movements : None/Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Gait pattern : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Severity of gait (1-3)	-	-	-	-	-	-	-	-	-	-	-	-	-
Mobility score : Normal	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6
Pupillary response : Response (Miosis)	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6	6/6

- Not applicable as gait pattern normal.

TABLE NO.O (Contd.)

SUMMARY OF DETAILED CLINICAL OBSERVATIONS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number : VI

Dose : 1000 mg/kg (Reversal)

Week	14	15	16	17
Number of animals observed	6	6	6	6
Number of animals within normal limit	6/6	6/6	6/6	6/6
Number of animals with significant deviation	0/6	0/6	0/6	0/6
Parameters				
Behavior in Home cage				
Awake	4/6	5/6	5/6	5/6
Engaged in apparently normal movement	2/6	1/6	1/6	1/6
Alterations Home cage : No alterations	6/6	6/6	6/6	6/6
Vocalizations : No vocalization	6/6	6/6	6/6	6/6
Respiration : Normal	6/6	6/6	6/6	6/6
Palpebral closer : Eyelids wide open	6/6	6/6	6/6	6/6
Reaction to removal				
Sits quietly and is easily removed	4/6	5/6	5/6	4/6
Vocalization without resistance	2/6	1/6	1/6	2/6
Reaction to handling				
Quiet with no resistance	4/6	4/6	4/6	5/6
Vocalization without resistance	2/6	2/6	2/6	1/6
Urination				
No urination during the observation	3/6	3/6	4/6	4/6
Urine present; quantity is not excessive	3/6	3/6	2/6	2/6
Defecation				
No defecation during the observation	3/6	4/6	4/6	4/6
Fecal boluses have normal consistency	3/6	2/6	2/6	2/6
Prominence of Eye : Normal	6/6	6/6	6/6	6/6
Lacrimation : No excess lacrimation	6/6	6/6	6/6	6/6
Salivation : No excess salivation	6/6	6/6	6/6	6/6
Piloerection : Absent	6/6	6/6	6/6	6/6
Examination of mucous membrane : Normal	6/6	6/6	6/6	6/6
Examination of skin/fur : Normal	6/6	6/6	6/6	6/6
Examination of natural orifices : Normal	6/6	6/6	6/6	6/6
Animal appearance : Clean and groomed	6/6	6/6	6/6	6/6
Stereotype behaviour : Absent	6/6	6/6	6/6	6/6
Bizzare behaviour : Absent	6/6	6/6	6/6	6/6
Rearing (No.) Mean	10.33	10.33	10.00	10.00
± S.D.	1.37	1.03	0.89	1.41
Clonic movements : None/Normal	6/6	6/6	6/6	6/6
Tonic movements : None/Normal	6/6	6/6	6/6	6/6
Gait pattern : Normal	6/6	6/6	6/6	6/6
Severity of gait (1-3)	-	-	-	-
Mobility score : Normal	6/6	6/6	6/6	6/6
Pupillary response : Response (Miosis)	6/6	6/6	6/6	6/6

- Not applicable as gait pattern normal.

TABLE NO.P

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Week : 13 and 17

Group Number		I	II	III	IV	V	VI
Dose		0 mg/kg	0 mg/kg (Rev.)	250 mg/kg	500 mg/kg	1000 mg/kg	1000 mg/kg (Rev.)
Number of animals observed		10	6	10	10	10	6
Number of animals within normal limit		10/10	6/6	10/10	10/10	10/10	6/6
Number of animals with significant deviation		0/10	0/6	0/10	0/10	0/10	0/6
Parameters							
Arousal level : Apparently normal		10/10	6/6	10/10	10/10	10/10	6/6
Visual response : Orienting response		10/10	6/6	10/10	10/10	10/10	6/6
Touch response : Orienting response		10/10	6/6	10/10	10/10	10/10	6/6
Auditory response : Orienting response		10/10	6/6	10/10	10/10	10/10	6/6
Tail pinch response : Orienting response		10/10	6/6	10/10	10/10	10/10	6/6
Visual placing response : Early extension of forelimbs to reach for the screen		10/10	6/6	10/10	10/10	10/10	6/6
Air righting response : Lands with all feet on ground		10/10	6/6	10/10	10/10	10/10	6/6
Grip Strength (kg) - Mean ± SD		1.112 ± 0.094	1.042 ± 0.107	1.175 ± 0.160	1.127 ± 0.056	1.123 ± 0.078	1.088 ± 0.110
Motor Activity - Mean ± SD	Interval '1'	421.30 ± 28.26	950.33 ± 471.02	394.80 ± 75.31	394.80 ± 106.91	482.40 ± 135.48	1008.00 ± 467.89
	Interval '2'	335.20 ± 109.73	355.50 ± 212.95	304.60 ± 92.14	329.20 ± 103.32	342.80 ± 72.09	389.33 ± 191.57
	Interval '3'	222.30 ± 101.47	209.00 ± 99.11	196.70 ± 94.78	168.00 ± 96.58	281.40 ± 70.70	212.83 ± 108.75

Rev. = Reversal

TABLE NO.P (Contd.)

SUMMARY OF FUNCTIONAL OBSERVATIONAL BATTERY

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Week : 13 and 17

Group Number		I	II	III	IV	V	VI
Dose		0 mg/kg	0 mg/kg (Rev.)	250 mg/kg	500 mg/kg	1000 mg/kg	1000 mg/kg (Rev.)
Number of animals observed		10	6	10	10	10	6
Number of animals within normal limit		10/10	6/6	10/10	10/10	10/10	6/6
Number of animals with significant deviation		0/10	0/6	0/10	0/10	0/10	0/6
Parameters							
Arousal level : Apparently normal		10/10	6/6	10/10	10/10	10/10	6/6
Visual response : Orienting response		10/10	6/6	10/10	10/10	10/10	6/6
Touch response : Orienting response		10/10	6/6	10/10	10/10	10/10	6/6
Auditory response : Orienting response		10/10	6/6	10/10	10/10	10/10	6/6
Tail pinch response : Orienting response		10/10	6/6	10/10	10/10	10/10	6/6
Visual placing response : Early extension of forelimbs to reach for the screen		10/10	6/6	10/10	10/10	10/10	6/6
Air righting response : Lands with all feet on ground		10/10	6/6	10/10	10/10	10/10	6/6
Grip Strength (kg) - Mean ± SD		1.059 ± 0.059	1.055 ± 0.055	1.019 ± 0.099	1.029 ± 0.127	0.941 ± 0.100	1.084 ± 0.097
Motor Activity - Mean ± SD	Interval '1'	605.20 ± 128.53	500.17 ± 249.03	543.50 ± 88.39	536.80 ± 63.74	539.70 ± 90.13	545.83 ± 73.04
	Interval '2'	481.40 ± 164.27	280.50 ± 112.93	441.30 ± 81.54	418.60 ± 85.65	425.70 ± 69.40	368.67 ± 156.29
	Interval '3'	376.60 ± 149.26	232.00 ± 105.59	362.30 ± 65.94	343.50 ± 82.03	343.10 ± 77.36	333.17 ± 61.03

Rev. = Reversal

TABLE NO.Q

GROUP MEAN - HAEMATOLOGY

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Day : 91 and 119

Group Number	Dose mg/kg		Hb (g/dL)	Total RBC (x 10^6 /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
I	0	Mean	15.48	8.50	39.01	46.06	18.30	39.74
		± SD	1.50	1.12	4.09	1.41	0.71	0.53
II	0 (Rev.)	Mean	14.15	7.68	40.27	52.47	18.43	35.10
		± SD	0.56	0.25	1.34	1.64	0.83	0.42
III	250	Mean	14.01**	7.89	35.61	45.15	17.77*	39.32
		± SD	0.60	0.38	1.30	0.65	0.19	0.40
IV	500	Mean	16.64*	9.08	42.08*	46.39	18.33	39.53
		± SD	0.65	0.50	1.53	1.72	0.87	0.45
V	1000	Mean	16.14	8.71	40.63	46.67	18.56	39.76
		± SD	0.73	0.44	1.71	0.84	0.43	0.38
VI	1000 (Rev.)	Mean	13.63	7.63	39.02	51.15	17.88	34.95
		± SD	1.16	0.60	3.14	1.03	0.57	0.50

Group Number	Dose mg/kg		Platelets (x 10^3 /µL)	Total WBC (x 10^3 /µL)	Differential %					Pt (Sec.)
					N	L	E	M	B	
I	0	Mean	338.60	14.33	19.00	79.20	1.50	0.30	0.00	15.80
		± SD	59.45	1.48	2.98	3.26	1.08	0.48	0.00	3.05
II	0 (Rev.)	Mean	333.83	13.97	20.67	75.50	1.67	2.17	0.00	15.17
		± SD	40.59	1.63	2.16	2.07	0.82	0.75	0.00	3.66
III	250	Mean	284.60	15.50	18.70	79.10	1.30	0.90	0.00	14.80
		± SD	31.94	2.56	2.87	3.18	0.95	0.74	0.00	2.66
IV	500	Mean	356.40	16.59**	19.00	78.90	1.30	0.80	0.00	16.20
		± SD	44.19	1.15	2.58	2.33	1.16	0.79	0.00	2.94
V	1000	Mean	336.10	14.94	18.70	79.40	1.10	0.80	0.00	15.10
		± SD	64.45	1.10	2.98	3.27	0.99	0.79	0.00	3.21
VI	1000 (Rev.)	Mean	286.17	14.48	18.00*	78.50*	1.83	1.67	0.00	16.00
		± SD	55.75	1.47	1.41	2.17	1.17	0.82	0.00	3.35

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils
RBC : Red Blood Corpuscles
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration
Pt. : Prothrombin time
L : Lymphocytes
M : Monocytes

Rev. = Reversal
* = Significant at 95% level of confidence ($p \leq 0.05$)
** = Significant at 99% level of confidence ($p \leq 0.01$)

TABLE NO.Q (Contd.)

GROUP MEAN - HAEMATOLOGY

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Day : 91 and 119

Group Number	Dose mg/kg		Hb (g/dL)	Total RBC (x 10^6 /µL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
I	0	Mean	15.41	7.88	37.99	48.22	19.56	40.55
		± SD	0.91	0.42	2.31	1.43	0.58	0.28
II	0 (Rev.)	Mean	14.28	7.31	40.35	55.20	19.57	35.43
		± SD	1.24	0.73	4.09	2.01	0.71	0.72
III	250	Mean	16.12	7.99	39.97	50.10**	20.25	40.39
		± SD	1.07	0.77	3.18	1.39	0.78	0.65
IV	500	Mean	15.63	7.89	38.41	48.71	19.84	40.71
		± SD	0.86	0.41	2.20	1.26	0.59	0.36
V	1000	Mean	15.66	7.97	38.33	48.13	19.69	40.87
		± SD	0.55	0.42	1.78	0.75	0.62	0.78
VI	1000 (Rev.)	Mean	15.38	7.62	43.05	56.52	20.25	35.78
		± SD	0.92	0.49	2.77	1.08	0.33	0.26

Group Number	Dose mg/kg		Platelets (x 10^3 /µL)	Total WBC (x 10^3 /µL)	Differential %					Pt (Sec.)
					N	L	E	M	B	
I	0	Mean	314.70	8.93	18.20	80.00	1.00	0.80	0.00	15.90
		± SD	22.32	2.28	2.74	2.75	0.82	0.79	0.00	2.92
II	0 (Rev.)	Mean	286.17	8.42	20.67	76.00	1.33	2.00	0.00	17.00
		± SD	52.15	2.14	1.63	1.41	0.82	0.63	0.00	2.37
III	250	Mean	313.30	9.90	19.00	79.50	0.90	0.60	0.00	14.80
		± SD	30.71	2.57	2.79	3.14	1.10	0.70	0.00	2.66
IV	500	Mean	301.00	15.78**	19.10	79.70	0.90	0.30	0.00	15.50
		± SD	43.96	1.88	2.42	2.16	0.88	0.48	0.00	3.03
V	1000	Mean	265.90**	11.43	19.10	79.60	0.80	0.50	0.00	15.10
		± SD	31.12	3.56	3.00	3.37	0.79	0.71	0.00	3.21
VI	1000 (Rev.)	Mean	268.50	11.80	18.33*	78.17*	1.50	2.00	0.00	15.83
		± SD	26.14	4.18	1.63	1.83	1.05	0.63	0.00	3.06

Hb : Hemoglobin
HCT : Hematocrit
MCH : Mean Corpuscular Hemoglobin
WBC : White Blood Corpuscles
N : Neutrophils
E : Eosinophils
B : Basophils
RBC : Red Blood Corpuscles
MCV : Mean Corpuscular Volume
MCHC : Mean Corpuscular Hemoglobin Concentration
Pt. : Prothrombin time
L : Lymphocytes
M : Monocytes

Rev. = Reversal
* = Significant at 95% level of confidence ($p \leq 0.05$)
** = Significant at 99% level of confidence ($p \leq 0.01$)

TABLE NO.R

GROUP MEAN - CLINICAL BIOCHEMISTRY

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Day : 91 and 119

Group Number	Dose mg/kg		Total Protein (g/dL)	BUN (mg/dL)	Urea (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
I	0	Mean	7.44	12.70	27.69	60.20	113.40	139.00	107.20
		± SD	0.36	1.06	2.31	10.13	12.68	49.73	18.83
II	0 (Rev.)	Mean	7.12	16.33	35.61	52.00	106.33	111.50	110.67
		± SD	0.45	2.07	4.50	9.23	10.86	22.76	29.60
III	250	Mean	7.32	12.70	27.69	52.10*	118.20	111.00	104.20
		± SD	0.35	0.82	1.79	6.12	13.86	16.45	17.11
IV	500	Mean	7.49	13.20	28.78	52.00*	118.10	117.00	97.80
		± SD	0.43	1.40	3.05	5.77	17.04	27.13	9.15
V	1000	Mean	6.99*	12.50	27.25	50.90*	106.70	124.30	86.60**
		± SD	0.37	1.08	2.35	4.70	13.41	23.13	7.24
VI	1000 (Rev.)	Mean	6.93	16.67	36.33	52.83	114.50	124.33	107.17
		± SD	0.22	1.37	2.98	10.87	13.37	23.34	32.73

Group Number	Dose mg/kg		Calcium (mmol/L)	Phospho-rous (mg/dL)	GGT (U/L)	Total Bilirubin (mg/dL)	Albumin (g/dL)	Globulin (g/dL)	Creatinine (mg/dL)
I	0	Mean	3.66	6.03	8.20	0.15	1.17	6.28	0.67
		± SD	0.28	0.89	0.92	0.03	0.11	0.32	0.06
II	0 (Rev.)	Mean	4.13	6.87	7.67	0.10	1.08	6.03	0.55
		± SD	0.13	1.90	0.82	0.03	0.13	0.39	0.11
III	250	Mean	3.56	6.78	8.10	0.14	1.15	6.16	0.73
		± SD	0.15	0.74	0.74	0.02	0.08	0.35	0.06
IV	500	Mean	3.59	6.11	8.90	0.13	1.25	6.24	0.78**
		± SD	0.11	0.71	0.74	0.03	0.12	0.45	0.06
V	1000	Mean	3.59	5.65	8.40	0.12	1.14	5.84	0.65
		± SD	0.11	0.53	0.97	0.02	0.09	0.39	0.04
VI	1000 (Rev.)	Mean	4.18	6.25	8.67	0.12	1.03	5.90	0.57
		± SD	0.14	0.58	0.82	0.03	0.07	0.25	0.08

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Aminotransferase
ALP : Alkaline Phosphatase
GGT : Gamma Glutamyl Transferase

Rev. = Reversal
* = Significant at 95% level of confidence ($p \leq 0.05$)
** = Significant at 99% level of confidence ($p \leq 0.01$)

TABLE NO.R (Contd.)

GROUP MEAN - CLINICAL BIOCHEMISTRY

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Day : 91 and 119

Group Number	Dose mg/kg		Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)
I	0	Mean	147.09	4.09	107.59	36.90	67.60
		± SD	3.20	0.47	8.48	6.03	7.52
II	0 (Rev.)	Mean	146.34	3.80	108.97	33.50	69.17
		± SD	0.98	0.18	1.88	3.39	19.06
III	250	Mean	146.72	4.31	110.32	32.10	67.80
		± SD	1.48	0.38	1.91	6.77	17.16
IV	500	Mean	146.69	4.00	109.67	38.80	78.20
		± SD	1.55	0.40	1.57	9.75	13.92
V	1000	Mean	146.23	4.08	109.95	32.10	74.50
		± SD	0.97	0.40	2.14	5.20	18.16
VI	1000 (Rev.)	Mean	146.06	4.28*	105.14*	31.83	75.17
		± SD	1.64	0.43	3.61	5.85	20.86

Rev. = Reversal
* = Significant at 95% level of confidence ($p \leq 0.05$)

TABLE NO.R (Contd.)

GROUP MEAN - CLINICAL BIOCHEMISTRY

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Day : 91 and 119

Group Number	Dose mg/kg		Total Protein (g/dL)	BUN (mg/dL)	Urea (mg/dL)	ALT (U/L)	AST (U/L)	ALP (U/L)	Glucose (mg/dL)
I	0	Mean	7.17	12.60	27.47	43.70	98.50	101.20	88.50
		± SD	0.48	1.51	3.28	5.17	6.67	15.58	12.12
II	0 (Rev.)	Mean	7.30	16.33	35.61	37.17	108.50	75.17	93.00
		± SD	0.35	1.37	2.98	4.54	26.28	13.24	11.93
III	250	Mean	7.40	12.30	26.81	45.10	97.90	79.90*	86.30
		± SD	0.41	1.70	3.71	9.59	14.72	21.13	7.76
IV	500	Mean	8.36**	14.20	30.96	48.90	116.80**	104.60	98.70
		± SD	0.81	1.03	2.25	4.38	11.14	12.77	11.94
V	1000	Mean	7.19	13.40	29.21	47.20	110.70*	84.90	75.40*
		± SD	0.37	2.27	4.95	6.63	10.57	15.57	9.71
VI	1000 (Rev.)	Mean	7.62	17.83	38.88	41.00	108.00	75.83	87.17
		± SD	0.34	1.72	3.75	5.97	14.63	12.69	6.08

Group Number	Dose mg/kg		Calcium (mmol/L)	Phospho-rous (mg/dL)	GGT (U/L)	Total Bilirubin (mg/dL)	Albumin (g/dL)	Globulin (g/dL)	Creatinine (mg/dL)
I	0	Mean	3.60	4.84	7.90	0.18	1.42	5.76	0.66
		± SD	0.12	0.63	1.37	0.05	0.20	0.37	0.07
II	0 (Rev.)	Mean	4.11	4.80	7.50	0.11	1.46	5.83	0.66
		± SD	0.09	1.08	0.84	0.02	0.14	0.30	0.07
III	250	Mean	3.50	5.48	7.50	0.12**	1.45	5.96	0.63
		± SD	0.18	0.64	0.53	0.01	0.16	0.33	0.11
IV	500	Mean	3.65	5.00	8.40	0.16	1.58	6.78**	0.62
		± SD	0.21	0.39	0.52	0.05	0.23	0.62	0.07
V	1000	Mean	3.56	4.97	7.70	0.10**	1.43	5.77	0.73*
		± SD	0.21	0.49	0.48	0.02	0.15	0.25	0.04
VI	1000 (Rev.)	Mean	4.09	4.90	6.83	0.11	1.45	6.18*	0.65
		± SD	0.08	0.85	1.60	0.02	0.13	0.22	0.10

BUN : Blood Urea Nitrogen
ALT : Alanine Aminotransferase
AST : Aspartate Aminotransferase
ALP : Alkaline Phosphatase
GGT : Gamma Glutamyl Transferase

Rev. = Reversal
* = Significant at 95% level of confidence ($p \leq 0.05$)
** = Significant at 99% level of confidence ($p \leq 0.01$)

TABLE NO.R (Contd.)

GROUP MEAN - CLINICAL BIOCHEMISTRY

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Day : 91 and 119

Group Number	Dose mg/kg		Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Total Cholesterol (mg/dL)	Triglycerides (mg/dL)
I	0	Mean	145.91	4.03	108.22	48.60	71.30
		± SD	0.81	0.35	2.44	10.47	30.58
II	0 (Rev.)	Mean	145.39	4.12	111.30	55.67	64.00
		± SD	0.97	0.51	1.42	15.45	25.23
III	250	Mean	146.48	4.31	109.56	50.20	75.70
		± SD	1.74	0.30	1.75	9.65	20.23
IV	500	Mean	146.30	4.26	105.05**	61.90**	71.90
		± SD	1.62	0.23	1.89	8.77	35.58
V	1000	Mean	146.37	4.23	105.68*	44.40	61.00
		± SD	1.38	0.20	2.00	7.68	25.02
VI	1000 (Rev.)	Mean	145.30	4.23	112.33	44.67	51.17
		± SD	0.55	0.25	4.15	12.66	10.48

Rev. = Reversal
* = Significant at 95% level of confidence ($p \leq 0.05$)
** = Significant at 99% level of confidence ($p \leq 0.01$)

TABLE NO.S

GROUP MEAN URINE ANALYSES

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Day : 86, 87 and 119

Group Number	Dose mg/kg		Volume (ml)	Glucose (mmol/L)	Bilirubin (mmol/L)	Ketones (mmol/L)	Sp.Gr. (g/L)	Occult Blood (caCELLS/µL)
I	0	Mean	7.90	-ve	-ve	-ve	1.018	-ve
		± SD	1.13	-ve	-ve	-ve	0.003	-ve
II	0 (Rev.)	Mean	8.95	-ve	-ve	-ve	1.017	-ve
		± SD	0.99	-ve	-ve	-ve	0.003	-ve
III	250	Mean	7.53	-ve	-ve	-ve	1.018	-ve
		± SD	1.47	-ve	-ve	-ve	0.003	-ve
IV	500	Mean	7.03	-ve	-ve	-ve	1.018	-ve
		± SD	1.01	-ve	-ve	-ve	0.003	-ve
V	1000	Mean	7.34	-ve	-ve	-ve	1.018	-ve
		± SD	1.00	-ve	-ve	-ve	0.003	-ve
VI	1000 (Rev.)	Mean	8.32	-ve	-ve	-ve	1.018	-ve
		± SD	0.86	-ve	-ve	-ve	0.003	-ve

Group Number	Dose mg/kg		pH	Urobilinogen (mmol/L)	Nitrite
I	0	Mean	7.35	-ve	-ve
		± SD	0.24	-ve	-ve
II	0 (Rev.)	Mean	7.42	-ve	-ve
		± SD	0.20	-ve	-ve
III	250	Mean	7.30	-ve	-ve
		± SD	0.26	-ve	-ve
IV	500	Mean	7.35	-ve	-ve
		± SD	0.24	-ve	-ve
V	1000	Mean	7.35	-ve	-ve
		± SD	0.24	-ve	-ve
VI	1000 (Rev.)	Mean	7.33	-ve	-ve
		± SD	0.26	-ve	-ve

Sp.Gr. : Specific gravity +ve : Positive -ve : Negative

Qualitative
Absent = 0
Trace = +
Small amount of analyte = ++
Moderate amount of analyte = +++
Large amount of analyte = ++++
Rev. = Reversal

TABLE NO.S (Contd.)

GROUP MEAN URINE ANALYSES

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Day : 87, 88 and 119

Group Number	Dose mg/kg		Volume (ml)	Glucose (mmol/L)	Bilirubin (mmol/L)	Ketones (mmol/L)	Sp.Gr. (g/L)	Occult Blood (caCELLS/µL)
I	0	Mean	5.87	-ve	-ve	-ve	1.017	-ve
		± SD	0.96	-ve	-ve	-ve	0.003	-ve
II	0 (Rev.)	Mean	8.15	-ve	-ve	-ve	1.017	-ve
		± SD	0.91	-ve	-ve	-ve	0.003	-ve
III	250	Mean	5.77	-ve	-ve	-ve	1.017	-ve
		± SD	0.96	-ve	-ve	-ve	0.002	-ve
IV	500	Mean	6.65	-ve	-ve	-ve	1.018	-ve
		± SD	1.05	-ve	-ve	-ve	0.003	-ve
V	1000	Mean	7.07*	-ve	-ve	-ve	1.018	-ve
		± SD	1.02	-ve	-ve	-ve	0.003	-ve
VI	1000 (Rev.)	Mean	7.73	-ve	-ve	-ve	1.018	-ve
		± SD	0.99	-ve	-ve	-ve	0.003	-ve

Group Number	Dose mg/kg		pH	Urobilinogen (mmol/L)	Nitrite
I	0	Mean	7.35	-ve	-ve
		± SD	0.24	-ve	-ve
II	0 (Rev.)	Mean	7.33	-ve	-ve
		± SD	0.26	-ve	-ve
III	250	Mean	7.35	-ve	-ve
		± SD	0.24	-ve	-ve
IV	500	Mean	7.35	-ve	-ve
		± SD	0.24	-ve	-ve
V	1000	Mean	7.25	-ve	-ve
		± SD	0.26	-ve	-ve
VI	1000 (Rev.)	Mean	7.42	-ve	-ve
		± SD	0.20	-ve	-ve

Sp.Gr. : Specific gravity +ve : Positive -ve : Negative

Qualitative
Absent = 0
Trace = +
Small amount of analyte = ++
Moderate amount of analyte = +++
Large amount of analyte = ++++
Rev. = Reversal
* = Significant at 95% level of confidence ($p \leq 0.05$)

TABLE NO.T

GROUP MEAN ABSOLUTE ORGAN WEIGHTS (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Day : 91 and 119

Group Number	Dose mg/kg		Terminal Body weight (g)	Brain	Liver	Kidneys	Adrenals	Testes
I	0	Mean	448.72	2.138	14.999	3.062	0.0585	3.315
		± SD	24.97	0.088	2.324	0.316	0.0182	0.208
II	0 (Rev.)	Mean	492.70	2.143	16.177	3.169	0.0554	3.263
		± SD	11.21	0.099	1.723	0.158	0.0072	0.152
III	250	Mean	469.49	2.177	15.717	3.304	0.0744	3.361
		± SD	29.85	0.140	2.467	0.326	0.0165	0.264
IV	500	Mean	450.88	2.135	13.874	2.869	0.0638	3.209
		± SD	25.78	0.082	1.465	0.251	0.0192	0.326
V	1000	Mean	457.83	2.134	14.547	2.990	0.0646	3.214
		± SD	26.16	0.089	1.414	0.204	0.0112	0.281
VI	1000 (Rev.)	Mean	490.27	2.146	15.244	3.191	0.0628	3.529
		± SD	23.81	0.118	0.941	0.360	0.0146	0.216

Group Number	Dose mg/kg		Heart	Spleen	Thymus	Epididymides
I	0	Mean	1.529	1.643	0.253	1.270
		± SD	0.186	0.204	0.063	0.068
II	0 (Rev.)	Mean	1.646	1.463	0.209	1.153
		± SD	0.136	0.241	0.059	0.076
III	250	Mean	1.632	1.472	0.282	1.245
		± SD	0.278	0.300	0.089	0.114
IV	500	Mean	1.627	1.618	0.236	1.121
		± SD	0.219	0.294	0.047	0.112
V	1000	Mean	1.605	1.635	0.256	1.125
		± SD	0.221	0.301	0.049	0.098
VI	1000 (Rev.)	Mean	1.519	1.453	0.234	1.191
		± SD	0.185	0.294	0.062	0.040

Rev. = Reversal

TABLE NO.T (Contd.)

GROUP MEAN ABSOLUTE ORGAN WEIGHTS (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Day : 91 and 119

Group Number	Dose mg/kg		Terminal Body weight (g)	Brain	Liver	Kidneys	Adrenals	Ovaries
I	0	Mean	275.12	1.994	8.073	1.773	0.0592	0.0874
		± SD	13.65	0.102	0.568	0.146	0.0083	0.0065
II	0 (Rev.)	Mean	291.83	2.081	9.188	1.764	0.0667	0.0768
		± SD	7.61	0.075	0.998	0.129	0.0158	0.0081
III	250	Mean	279.80	1.927	8.344	1.705	0.0647	0.0731
		± SD	11.45	0.087	0.676	0.139	0.0078	0.0140
IV	500	Mean	279.78	2.021	9.033	1.834	0.0732	0.0865
		± SD	19.36	0.079	0.963	0.182	0.0099	0.0073
V	1000	Mean	282.02	1.966	8.036	1.745	0.0646	0.0827
		± SD	16.33	0.108	1.057	0.130	0.0089	0.0125
VI	1000 (Rev.)	Mean	283.80	2.119	8.850	1.874	0.0727	0.0846
		± SD	12.37	0.067	0.590	0.148	0.0106	0.0085

Group Number	Dose mg/kg		Heart	Spleen	Thymus	Uterus
I	0	Mean	1.035	0.998	0.259	0.410
		± SD	0.139	0.224	0.057	0.088
II	0 (Rev.)	Mean	1.040	0.911	0.243	0.455
		± SD	0.104	0.077	0.055	0.088
III	250	Mean	0.987	0.992	0.254	0.445
		± SD	0.130	0.096	0.046	0.108
IV	500	Mean	1.087	1.060	0.243	0.399
		± SD	0.127	0.051	0.042	0.081
V	1000	Mean	1.074	0.964	0.277	0.417
		± SD	0.079	0.331	0.051	0.062
VI	1000 (Rev.)	Mean	1.019	1.036	0.215	0.384
		± SD	0.118	0.150	0.011	0.039

Rev. = Reversal

TABLE NO.U

GROUP MEAN RELATIVE ORGAN WEIGHTS (%)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Day : 91 and 119

Group Number	Dose mg/kg		Terminal Body weight (g)	Brain	Liver	Kidneys	Adrenals	Testes
I	0	Mean	448.72	0.477	3.329	0.682	0.0130	0.741
		± SD	24.97	0.029	0.367	0.049	0.0039	0.062
II	0 (Rev.)	Mean	492.70	0.435	3.288	0.643	0.0113	0.663
		± SD	11.21	0.021	0.389	0.037	0.0016	0.038
III	250	Mean	469.49	0.465	3.342	0.705	0.0158	0.718
		± SD	29.85	0.034	0.431	0.070	0.0029	0.062
IV	500	Mean	450.88	0.475	3.081	0.637	0.0143	0.714
		± SD	25.78	0.030	0.320	0.053	0.0046	0.087
V	1000	Mean	457.83	0.468	3.184	0.654	0.0141	0.703
		± SD	26.16	0.041	0.331	0.046	0.0019	0.054
VI	1000 (Rev.)	Mean	490.27	0.438	3.110	0.651	0.0128	0.721
		± SD	23.81	0.019	0.146	0.064	0.0031	0.061

Group Number	Dose mg/kg		Heart	Spleen	Thymus	Epididymides
I	0	Mean	0.341	0.366	0.057	0.283
		± SD	0.036	0.038	0.017	0.012
II	0 (Rev.)	Mean	0.334	0.297	0.042	0.234
		± SD	0.030	0.048	0.013	0.019
III	250	Mean	0.347	0.314	0.060	0.266
		± SD	0.051	0.068	0.018	0.029
IV	500	Mean	0.361	0.360	0.052	0.250*
		± SD	0.050	0.070	0.011	0.030
V	1000	Mean	0.351	0.356	0.056	0.246**
		± SD	0.048	0.055	0.011	0.025
VI	1000 (Rev.)	Mean	0.309	0.296	0.047	0.243
		± SD	0.026	0.057	0.010	0.011

Rev. = Reversal
* = Significant at 95% level of confidence ($p \leq 0.05$)
** = Significant at 99% level of confidence ($p \leq 0.01$)

TABLE NO.U (Contd.)

GROUP MEAN RELATIVE ORGAN WEIGHTS (%)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Day : 91 and 119

Group Number	Dose mg/kg		Terminal Body weight (g)	Brain	Liver	Kidneys	Adrenals	Ovaries
I	0	Mean	275.12	0.727	2.940	0.646	0.0216	0.0319
		± SD	13.65	0.052	0.245	0.067	0.0031	0.0033
II	0 (Rev.)	Mean	291.83	0.714	3.146	0.605	0.0229	0.0263
		± SD	7.61	0.037	0.307	0.046	0.0054	0.0029
III	250	Mean	279.80	0.690	2.983	0.610	0.0232	0.0262*
		± SD	11.45	0.043	0.226	0.048	0.0031	0.0052
IV	500	Mean	279.78	0.724	3.232	0.655	0.0262**	0.0311
		± SD	19.36	0.042	0.313	0.041	0.0031	0.0036
V	1000	Mean	282.02	0.699	2.850	0.619	0.0228	0.0294
		± SD	16.33	0.047	0.336	0.041	0.0023	0.0048
VI	1000 (Rev.)	Mean	283.80	0.748	3.119	0.660	0.0256	0.0299
		± SD	12.57	0.051	0.160	0.049	0.0031	0.0041

Group Number	Dose mg/kg		Heart	Spleen	Thymus	Uterus
I	0	Mean	0.378	0.363	0.094	0.149
		± SD	0.058	0.081	0.018	0.030
II	0 (Rev.)	Mean	0.357	0.312	0.083	0.156
		± SD	0.036	0.019	0.020	0.031
III	250	Mean	0.354	0.355	0.091	0.160
		± SD	0.060	0.035	0.018	0.043
IV	500	Mean	0.389	0.380	0.087	0.143
		± SD	0.043	0.026	0.017	0.030
V	1000	Mean	0.381	0.339	0.099	0.148
		± SD	0.025	0.100	0.020	0.024
VI	1000 (Rev.)	Mean	0.359	0.365*	0.076	0.135
		± SD	0.039	0.048	0.006	0.015

Rev. = Reversal
* = Significant at 95% level of confidence ($p \leq 0.05$)
** = Significant at 99% level of confidence ($p \leq 0.01$)

TABLE NO.V

SUMMARY OF GROSS PATHOLOGY FINDINGS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex - Male

Site and lesion observed	Group Number	I	II	III	IV	V	VI
	Dose (mg/kg)	0	0 (Rev.)	250	500	1000	1000 (Rev.)
No Abnormality Detected		1-10	21-26	33-42	53-62	73-82	93-98

Rev. = Reversal

TABLE NO.V (Contd.)

SUMMARY OF GROSS PATHOLOGY FINDINGS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex - Female

Site and lesion observed	Group Number	I	II	III	IV	V	VI
	Dose (mg/kg)	0	0 (Rev.)	250	500	1000	1000 (Rev.)
No Abnormality Detected		11-20	27-32	43-52	63-72	83-92	99-104

Rev. = Reversal

TABLE NO.W

SUMMARY OF HISTOPATHOLOGY FINDINGS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male
Days : All

Fates : All

Dose		0 mg/kg	1000 mg/kg
Number of Animals :		10	10
		# AWA	# AWA
Adrenals	# Ex	10	10
Vacuolation		1	1
Dilatation		1	0
Aorta	# Ex	10	10
		NAD	NAD
Brain (cerebrum, cerebellum and pons)	# Ex	10	10
		NAD	NAD
Caecum	# Ex	10	10
		NAD	NAD
Colon	# Ex	10	10
		NAD	NAD
Duodenum	# Ex	10	10
		NAD	NAD
Epididymides	# Ex	10	10
		NAD	NAD
Eyes	# Ex	10	10
		NAD	NAD
Heart	# Ex	10	10
		NAD	NAD
Ileum	# Ex	10	10
		NAD	NAD
Jejunum	# Ex	10	10
		NAD	NAD
Kidneys	# Ex	10	10
Haemorrhages		5	4
Dilatation, tubular		3	1
Liver	# Ex	10	10
Infiltration		4	4
Lungs	# Ex	10	10
Haemorrhages		10	10
Histiocytosis		1	4
Mesenteric Lymphnodes	# Ex	10	10
		NAD	NAD
Muscles - Skeletal muscle	# Ex	10	10
		NAD	NAD

# AWA = Number of animals with abnormality in the group.
# Ex = Number of animals examined
NAD = No Abnormality Detected

TABLE NO.W (Contd.)

SUMMARY OF HISTOPATHOLOGY FINDINGS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male Fates : All
Days : All

Dose		0 mg/kg	1000 mg/kg
Number of Animals :		10	10
		# AWA	# AWA
Oesophagus	# Ex	10	10
		NAD	NAD
Pancreas	# Ex	10	10
		NAD	NAD
Pharyngeal Lymphnodes	# Ex	10	10
		NAD	NAD
Pituitary	# Ex	10	10
		NAD	NAD
Prostate	# Ex	10	10
		NAD	NAD
Rectum	# Ex	10	10
		NAD	NAD
Salivary Gland	# Ex	10	10
		NAD	NAD
Sciatic nerve	# Ex	10	10
		NAD	NAD
Seminal vesicles	# Ex	10	10
		NAD	NAD
Skin with Mammary Gland	# Ex	10	10
		NAD	NAD
Spleen	# Ex	10	10
Haemosiderosis		10	10
Spinal Cord (Cervical, mid thoracic and lumbar)	# Ex	10	10
		NAD	NAD
Sternum with bone marrow	# Ex	10	10
		NAD	NAD
Stomach	# Ex	10	10
		NAD	NAD
Testes	# Ex	10	10
		NAD	NAD
Thymus	# Ex	10	10
Haemorrhages		1	1
Thyroid / Parathyroid	# Ex	10	10
Ultimobranchial cyst		1	0
Trachea	# Ex	10	10
		NAD	NAD
Urinary Bladder	# Ex	10	10
Seminal Coagulum		2	1

# AWA = Number of animals with abnormality in the group.
# Ex = Number of animals examined
NAD = No Abnormality Detected

TABLE NO.W (Contd.)

SUMMARY OF HISTOPATHOLOGY FINDINGS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female
Days : All

Fates : All

Dose		0 mg/kg	1000 mg/kg
Number of Animals :		10	10
		# AWA	# AWA
Adrenals	# Ex	10	10
Dilatation		2	1
Aorta	# Ex	10	10
		NAD	NAD
Brain (cerebrum, cerebellum and pons)	# Ex	10	10
		NAD	NAD
Caecum	# Ex	10	10
		NAD	NAD
Colon	# Ex	10	10
		NAD	NAD
Duodenum	# Ex	10	10
		NAD	NAD
Eyes	# Ex	10	10
		NAD	NAD
Heart	# Ex	10	10
		NAD	NAD
Ileum	# Ex	10	10
		NAD	NAD
Jejunum	# Ex	10	10
		NAD	NAD
Kidneys	# Ex	10	10
Infiltration		1	1
Haemorrhages		5	4
Dilatation		1	1
Liver	# Ex	10	10
Infiltration		3	5
Lungs	# Ex	10	10
Haemorrhages		10	10
Histiocytosis		2	2
Mesenteric Lymphnodes	# Ex	10	10
		NAD	NAD
Muscles - Skeletal muscle	# Ex	10	10
		NAD	NAD
Muscles - Skeletal muscle	# Ex	10	10
		NAD	NAD

# AWA = Number of animals with abnormality in the group.
# Ex = Number of animals examined
NAD = No Abnormality Detected

TABLE NO.W (Contd.)

SUMMARY OF HISTOPATHOLOGY FINDINGS

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female
Days : All

Fates : All

Dose		0 mg/kg	1000 mg/kg
Number of Animals :		10	10
		# AWA	# AWA
Oesophagus	# Ex	10	10
		NAD	NAD
Ovaries	# Ex	10	10
		NAD	NAD
Pancreas	# Ex	10	10
		NAD	NAD
Pharyngeal Lymphnodes	# Ex	10	10
		NAD	NAD
Pituitary	# Ex	10	10
		NAD	NAD
Rectum	# Ex	10	10
		NAD	NAD
Salivary Gland	# Ex	10	10
		NAD	NAD
Sciatic nerve	# Ex	10	10
		NAD	NAD
Skin with Mammary Gland	# Ex	10	10
		NAD	NAD
Spleen	# Ex	10	10
Haemosiderosis		10	10
Congestion		1	0
Spinal Cord (Cervical, mid thoracic and lumbar)	# Ex	10	10
		NAD	NAD
Sternum with bone marrow	# Ex	10	10
		NAD	NAD
Stomach	# Ex	10	10
		NAD	NAD
Thymus	# Ex	10	10
		NAD	NAD
Thyroid / Parathyroid	# Ex	10	10
Ultimobranchial cyst		0	1
Trachea	# Ex	10	10
		NAD	NAD
Urinary Bladder	# Ex	10	10
		NAD	NAD
Uterus	# Ex	10	10
Infiltration		1	1
Dilatation		1	1

# AWA = Number of animals with abnormality in the group.
# Ex = Number of animals examined
NAD = No Abnormality Detected

APPENDIX NO.VI

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : I

Dose : 0 mg/kg

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
1	111.5	117.4	177.3	252.7	324.2	352.0	391.0
2	116.1	121.9	166.5	246.4	300.1	325.1	363.3
3	118.2	123.4	183.5	239.3	279.7	308.7	349.0
4	122.0	127.3	175.1	251.0	298.0	335.6	370.6
5	125.0	131.4	184.0	245.4	312.3	345.0	368.9
6	127.6	133.4	180.0	250.5	307.6	343.5	369.8
7	133.7	136.0	189.8	250.5	299.5	327.3	349.5
8	134.6	141.2	199.8	257.8	305.3	335.4	365.6
9	137.5	142.1	198.4	256.3	330.3	362.6	400.0
10	141.6	146.4	199.4	248.1	322.1	356.1	384.2

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
1	423.4	453.7	483.9	492.8	500.1	513.7	518.0	525.5
2	392.4	420.5	456.1	463.5	475.7	484.7	488.5	493.7
3	364.2	382.4	420.8	434.1	448.5	452.2	457.8	462.1
4	383.8	398.9	401.0	419.0	436.6	442.3	447.3	451.8
5	383.1	392.2	411.1	427.5	438.7	448.6	451.9	456.7
6	381.4	396.6	413.4	428.3	442.5	450.6	455.7	463.5
7	360.9	368.2	375.4	389.0	406.7	421.7	425.9	435.6
8	378.8	393.5	412.1	427.4	442.4	455.2	461.6	468.0
9	408.5	425.5	440.3	455.2	465.3	472.7	475.8	481.0
10	403.3	412.5	412.6	426.4	437.8	446.2	452.5	458.5

APPENDIX NO.VI (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : I

Dose : 0 mg/kg

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
11	102.1	106.2	150.5	190.8	217.7	232.4	244.3
12	106.7	109.1	147.7	174.1	200.9	215.9	230.5
13	115.3	118.3	158.6	189.3	221.6	238.3	258.5
14	118.3	122.0	161.3	201.3	222.8	235.8	248.8
15	121.3	125.0	165.8	207.4	232.8	250.9	262.0
16	123.4	127.6	155.4	182.3	208.3	250.0	266.3
17	126.7	129.3	159.7	194.0	228.9	248.6	256.4
18	127.5	130.5	183.0	216.2	249.4	265.4	280.0
19	128.0	132.1	163.9	194.0	218.9	233.8	243.8
20	128.6	131.7	175.2	208.4	226.8	239.1	249.3

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
11	255.2	257.7	261.5	265.9	267.4	269.8	271.6	273.3
12	239.0	243.0	249.4	256.9	257.1	260.7	263.2	264.9
13	270.5	274.9	277.3	284.3	285.4	288.8	290.2	292.6
14	258.4	265.8	269.9	273.3	278.2	280.3	281.8	283.1
15	268.6	271.3	281.6	287.0	289.2	291.3	296.5	299.4
16	275.6	277.9	281.4	289.0	292.2	295.1	297.2	302.5
17	261.3	272.9	277.9	283.2	286.3	287.8	288.2	290.3
18	287.1	287.7	292.0	299.4	300.5	302.0	305.0	308.3
19	250.6	258.6	267.9	273.7	276.2	278.8	280.9	283.7
20	258.6	261.9	265.5	270.1	272.7	273.8	275.2	279.1

APPENDIX NO.VI (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : II

Dose : 0 mg/kg (Reversal)

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
21	111.8	117.9	178.4	225.0	297.4	325.2	364.1
22	114.0	120.2	180.1	240.3	308.5	352.7	376.7
23	118.4	125.3	185.6	227.7	309.8	339.7	369.5
24	122.8	129.2	179.7	246.0	305.2	334.1	360.5
25	125.0	131.8	180.6	248.4	311.0	339.3	380.2
26	144.0	150.2	198.6	256.0	317.5	351.1	384.4

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
21	384.0	406.4	428.7	438.2	452.4	458.3	462.2	469.2
22	399.1	415.2	431.7	447.9	461.0	467.4	475.9	484.6
23	381.1	394.4	420.4	438.0	466.2	475.4	481.7	490.5
24	378.4	389.3	421.3	435.8	449.8	455.6	460.1	468.0
25	400.4	416.7	433.3	449.7	459.1	462.2	467.8	476.3
26	399.0	413.0	444.4	458.2	475.4	486.0	492.2	500.0

Animal No.	WEEKS			
	14	15	16	17
21	476.6	484.0	494.9	501.1
22	493.0	501.2	513.1	520.6
23	497.5	506.6	517.8	524.2
24	476.5	485.2	493.4	501.5
25	481.8	491.9	500.1	506.6
26	507.3	514.2	523.3	527.6

APPENDIX NO.VI (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : II

Dose : 0 mg/kg (Reversal)

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
27	102.6	106.0	147.6	185.0	203.1	234.1	244.2
28	105.3	107.8	157.6	198.9	224.3	249.7	258.7
29	115.9	119.3	151.9	191.5	211.8	233.2	243.9
30	118.3	121.6	162.5	200.8	221.9	240.7	253.4
31	122.5	125.3	160.4	198.1	222.9	234.3	247.8
32	129.4	132.2	164.1	203.8	228.7	241.3	253.7

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
27	261.2	265.7	270.4	275.9	277.1	278.6	280.5	286.1
28	270.7	273.2	279.3	287.5	289.4	293.0	295.7	298.9
29	261.6	270.8	275.7	280.1	282.7	284.7	287.2	290.3
30	263.2	273.6	278.1	285.1	287.2	288.8	290.3	294.8
31	251.3	253.3	258.6	265.5	267.6	270.2	273.2	276.2
32	260.9	260.3	267.7	273.7	276.3	277.5	279.2	283.8

Animal No.	WEEKS			
	14	15	16	17
27	289.0	293.4	298.1	303.2
28	303.6	307.1	311.7	316.3
29	295.2	299.5	305.0	309.5
30	298.5	302.9	307.1	312.0
31	282.2	287.9	292.4	298.3
32	287.5	291.5	295.5	297.4

APPENDIX NO.VI (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : III

Dose : 250 mg/kg

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
33	112.5	117.4	176.1	229.2	296.1	326.4	354.2
34	114.1	122.0	180.8	235.3	300.2	330.0	349.0
35	116.9	124.3	174.0	231.9	294.1	325.7	367.5
36	123.1	129.7	176.7	248.0	306.7	332.2	374.3
37	125.6	133.7	185.6	246.9	304.1	329.7	350.5
38	129.2	136.0	196.1	268.1	325.6	365.8	380.0
39	131.4	138.3	199.3	268.7	331.3	364.1	382.2
40	135.8	142.3	197.0	275.5	336.5	366.5	400.7
41	139.0	145.8	196.0	260.6	326.3	360.6	395.4
42	143.0	150.0	199.0	279.2	351.8	394.1	422.6

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
33	371.4	390.2	417.2	431.9	444.2	452.2	460.4	465.9
34	357.4	365.7	381.2	396.2	408.7	417.3	425.3	429.7
35	394.3	408.9	428.2	441.2	452.9	461.2	466.8	472.1
36	401.5	416.4	435.4	450.1	462.9	469.0	477.7	483.5
37	369.8	376.7	383.5	451.9	472.3	477.4	483.0	489.8
38	424.2	454.0	489.6	495.8	506.0	515.6	520.0	525.5
39	417.3	435.7	462.0	469.9	481.8	488.0	492.2	497.5
40	424.0	438.8	460.8	473.5	481.3	489.9	495.9	502.6
41	415.5	425.3	454.0	471.5	488.3	497.7	502.6	512.4
42	443.8	465.9	491.7	499.8	510.6	517.4	523.3	528.6

APPENDIX NO.VI (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : III

Dose : 250 mg/kg

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
43	103.4	107.6	147.6	178.3	200.9	221.9	229.7
44	106.0	110.3	153.9	190.6	218.7	240.9	259.2
45	108.3	112.2	146.0	193.2	229.8	250.6	267.4
46	118.5	122.3	154.2	194.2	229.3	254.0	269.8
47	122.8	127.7	162.7	196.3	217.4	233.5	247.0
48	123.6	128.3	153.4	186.3	212.9	231.0	246.1
49	125.8	129.2	166.7	208.9	230.5	249.2	267.3
50	127.7	129.9	167.9	204.1	221.9	248.8	260.4
51	128.0	132.8	166.7	205.0	225.1	247.2	260.1
52	129.3	132.2	161.1	188.5	220.1	240.7	256.4

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
43	239.4	252.8	255.7	261.5	262.4	265.9	267.1	270.6
44	265.9	269.1	274.0	279.9	280.2	282.5	285.6	287.7
45	269.5	274.2	280.4	288.6	290.4	293.0	295.5	300.4
46	274.1	279.3	286.1	291.8	291.9	293.3	296.1	298.6
47	262.3	265.3	269.6	273.9	276.3	278.7	281.2	282.3
48	262.5	267.7	270.2	277.8	278.4	280.3	282.5	286.6
49	273.6	281.8	293.4	297.6	299.6	301.6	305.3	307.6
50	273.0	273.7	280.3	287.8	290.3	292.3	294.2	297.0
51	268.7	272.8	276.0	281.5	283.3	285.1	286.7	288.0
52	265.7	268.7	272.8	278.6	280.3	282.5	286.1	288.7

APPENDIX NO.VI (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : IV

Dose : 500 mg/kg

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
53	112.8	119.8	175.4	244.1	319.1	346.3	385.9
54	114.7	122.1	181.9	254.0	322.0	351.4	400.7
55	117.3	124.1	182.6	255.4	323.3	360.9	387.8
56	118.6	125.1	185.5	254.0	317.2	343.1	361.2
57	126.8	132.8	191.7	260.3	316.8	342.2	366.7
58	129.8	136.8	192.4	252.8	321.6	346.5	367.5
59	131.9	138.0	189.1	250.0	295.4	318.8	335.7
60	134.0	141.2	181.0	226.5	286.1	300.7	325.7
61	139.4	145.5	196.0	253.9	324.2	348.6	374.3
62	139.8	146.6	202.4	276.6	350.5	368.2	385.0

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
53	403.3	413.7	433.2	448.4	463.3	475.3	485.4	490.3
54	420.8	444.5	451.1	468.1	483.0	488.1	495.3	503.7
55	401.2	427.5	458.3	473.2	486.0	495.2	501.7	510.6
56	377.7	390.1	397.4	413.9	429.5	433.3	441.8	450.4
57	383.5	396.9	423.7	440.2	453.4	460.4	468.2	472.2
58	384.4	393.2	421.2	436.9	447.8	458.0	463.8	469.0
59	351.2	361.7	385.0	406.9	419.7	422.1	429.3	435.5
60	335.8	349.0	388.5	397.5	422.9	428.1	435.3	441.7
61	390.6	398.8	410.8	424.2	438.4	440.8	447.6	452.5
62	399.4	428.9	445.2	457.3	468.4	472.3	480.9	485.0

APPENDIX NO.VI (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : IV

Dose : 500 mg/kg

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
63	103.6	106.8	141.0	173.9	211.6	223.2	245.4
64	106.0	109.6	156.3	201.5	230.0	255.3	279.5
65	110.7	114.1	155.0	191.0	220.4	234.1	247.0
66	116.1	119.5	160.0	202.0	229.7	267.3	283.6
67	122.9	124.1	153.6	187.7	209.9	225.1	244.2
68	123.7	126.4	163.9	194.0	213.7	240.0	252.7
69	125.9	128.5	149.8	186.6	212.2	247.3	256.9
70	126.7	129.4	171.9	214.0	228.1	252.2	262.5
71	128.0	132.0	170.1	202.9	232.9	274.0	285.2
72	128.2	133.9	172.5	205.5	228.3	245.1	255.5

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
63	252.4	259.8	264.3	269.5	270.4	273.5	277.6	279.7
64	286.0	288.5	290.0	295.5	300.4	303.2	307.7	310.3
65	252.2	257.7	263.7	270.0	272.5	275.1	277.5	281.5
66	287.1	294.0	297.9	302.8	303.3	305.3	307.7	310.5
67	249.6	251.2	256.1	263.9	265.3	267.9	269.1	272.5
68	256.0	259.4	263.6	272.2	273.1	276.6	280.3	283.5
69	263.2	266.0	271.8	278.2	280.4	283.0	285.8	287.4
70	267.1	268.7	271.8	276.7	278.3	280.6	282.4	284.3
71	292.9	307.9	316.5	321.0	322.0	324.2	326.3	329.7
72	261.1	262.9	266.7	270.7	272.4	274.3	276.6	279.8

APPENDIX NO.VI (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : V

Dose : 1000 mg/kg

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
73	113.1	120.8	156.7	217.2	273.6	300.0	315.6
74	115.4	122.7	164.2	236.0	300.8	320.2	354.3
75	117.5	124.3	183.8	261.1	330.9	371.1	425.6
76	119.9	125.5	176.8	240.5	300.2	327.0	359.3
77	124.3	129.3	190.1	257.7	323.7	355.2	401.5
78	131.0	137.1	189.1	255.3	317.8	343.5	375.9
79	132.8	139.1	198.6	258.8	324.1	350.7	368.3
80	134.7	140.5	195.6	250.9	330.0	355.2	395.2
81	136.5	142.8	197.3	252.7	313.9	350.6	381.0
82	140.8	147.3	203.0	267.2	331.1	360.1	390.8

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
73	325.8	352.5	387.7	402.5	413.0	419.3	423.7	431.0
74	370.5	397.5	421.1	435.7	444.7	450.4	455.5	460.4
75	451.6	469.8	482.6	496.6	501.9	506.0	512.0	517.6
76	372.6	398.9	422.6	443.3	454.6	461.0	468.8	472.6
77	428.3	451.9	461.2	472.0	486.1	489.5	492.7	498.5
78	388.3	404.2	429.6	443.6	454.6	461.9	467.4	473.1
79	378.6	387.8	421.2	438.6	447.8	452.3	460.0	465.9
80	415.2	436.6	468.2	486.1	496.6	503.6	508.9	513.3
81	396.2	404.2	425.2	443.9	454.5	459.5	463.4	470.1
82	402.4	414.4	435.2	453.9	467.1	472.3	476.4	482.0

APPENDIX NO.VI (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : V

Dose : 1000 mg/kg

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
83	104.2	107.8	145.3	188.7	219.8	245.1	268.2
84	106.3	109.1	147.3	186.8	221.7	244.0	257.6
85	113.3	116.1	167.3	202.6	225.2	258.6	286.7
86	116.4	120.1	161.1	198.1	222.5	265.4	285.0
87	119.9	123.1	157.2	195.4	216.1	228.3	240.3
88	124.5	127.1	168.7	204.1	224.1	245.8	255.1
89	125.9	129.4	166.8	202.2	223.1	233.1	247.1
90	127.1	131.4	165.7	203.6	233.2	251.6	263.2
91	127.7	131.7	159.4	200.4	225.2	244.1	251.4
92	128.3	133.7	166.4	205.3	233.1	247.7	259.9

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
83	273.5	275.9	277.5	283.8	286.4	289.3	292.1	294.5
84	270.3	271.5	276.4	281.3	282.4	286.4	287.2	290.7
85	292.4	294.9	304.1	308.1	309.2	312.5	315.7	318.8
86	293.1	296.4	310.2	316.8	318.7	320.6	323.5	326.3
87	246.7	250.2	254.1	260.6	262.1	265.3	271.4	274.6
88	258.7	261.8	268.7	276.5	278.4	280.2	282.4	283.6
89	254.1	257.4	262.2	266.8	269.0	271.7	275.0	277.5
90	269.2	274.2	281.4	288.1	289.0	292.3	293.7	296.7
91	263.5	266.3	271.7	276.1	277.4	279.9	281.7	284.3
92	264.4	267.0	272.0	278.0	280.2	283.0	285.7	289.3

APPENDIX NO.VI (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group : VI

Dose : 1000 mg/kg (Reversal)

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
93	113.5	119.5	174.4	232.2	304.1	330.0	355.4
94	116.2	122.8	180.7	239.8	319.3	348.3	385.0
95	118.1	125.0	186.2	243.0	306.5	356.6	411.5
96	121.5	127.5	188.1	256.1	318.9	344.0	367.9
97	124.9	131.0	173.4	231.0	300.3	338.7	352.4
98	144.2	150.0	198.5	266.1	327.8	356.3	382.9

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
93	373.1	396.0	418.9	432.7	443.7	449.4	453.4	463.0
94	402.0	413.0	437.9	456.9	468.7	473.2	479.0	483.9
95	435.4	460.1	483.5	496.4	507.4	513.5	517.3	524.3
96	376.7	386.8	409.4	422.0	433.5	441.1	447.6	455.2
97	369.4	382.5	410.5	427.9	439.0	446.9	451.3	461.0
98	399.7	417.3	437.4	455.9	468.7	472.9	477.5	484.6

Animal No.	WEEKS			
	14	15	16	17
93	472.2	478.5	486.1	492.6
94	493.4	501.0	512.7	519.5
95	532.8	538.9	547.7	554.1
96	465.6	472.5	483.9	490.6
97	469.8	475.6	487.3	495.1
98	492.1	497.2	509.3	514.6

APPENDIX NO.VI (Contd.)

INDIVIDUAL ANIMAL - BODY WEIGHT (g)

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group : VI

Dose : 1000 mg/kg (Reversal)

Animal No.	WEEKS						
	0	Day 1	1	2	3	4	5
99	104.8	108.6	147.8	190.4	219.2	233.5	260.0
100	106.4	110.6	150.8	187.9	207.0	227.4	235.6
101	114.3	118.5	151.1	193.5	216.7	232.7	244.2
102	117.6	121.3	154.1	183.2	205.2	223.0	245.6
103	120.1	125.3	160.1	205.7	231.4	247.0	257.3
104	129.7	133.7	169.1	205.8	232.9	242.1	253.1

Animal No.	WEEKS							
	6	7	8	9	10	11	12	13
99	278.4	281.9	284.2	289.1	291.2	293.4	295.4	301.4
100	241.0	243.7	247.0	254.1	256.4	258.3	260.4	264.4
101	251.9	257.9	261.7	269.0	271.1	272.7	273.8	276.3
102	254.2	256.6	266.2	271.7	273.4	275.1	278.8	281.6
103	263.2	265.4	269.9	275.0	277.3	280.2	282.6	286.7
104	260.5	262.3	267.3	271.1	272.1	275.5	277.5	284.4

Animal No.	WEEKS			
	14	15	16	17
99	306.5	310.5	314.4	318.6
100	267.9	269.9	274.9	280.2
101	280.1	285.0	289.4	292.8
102	285.3	288.8	294.1	299.2
103	292.5	294.9	299.4	302.9
104	288.2	291.1	294.2	297.2

APPENDIX NO.VII

INDIVIDUAL ANIMAL - OPHTHALMOSCOPIC EXAMINATION

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male Day : 0

Gr. No.	Dose mg/kg	Animal No.	Ophthalmoscopic Finding
I	0	1	No Abnormality Detected
		2	No Abnormality Detected
		3	No Abnormality Detected
		4	No Abnormality Detected
		5	No Abnormality Detected
		6	No Abnormality Detected
		7	No Abnormality Detected
		8	No Abnormality Detected
		9	No Abnormality Detected
		10	No Abnormality Detected
II	0 (Reversal)	21	No Abnormality Detected
		22	No Abnormality Detected
		23	No Abnormality Detected
		24	No Abnormality Detected
		25	No Abnormality Detected
		26	No Abnormality Detected
III	250	33	No Abnormality Detected
		34	No Abnormality Detected
		35	No Abnormality Detected
		36	No Abnormality Detected
		37	No Abnormality Detected
		38	No Abnormality Detected
		39	No Abnormality Detected
		40	No Abnormality Detected
		41	No Abnormality Detected
		42	No Abnormality Detected
IV	500	53	No Abnormality Detected
		54	No Abnormality Detected
		55	No Abnormality Detected
		56	No Abnormality Detected
		57	No Abnormality Detected
		58	No Abnormality Detected
		59	No Abnormality Detected
		60	No Abnormality Detected
		61	No Abnormality Detected
		62	No Abnormality Detected

APPENDIX NO.VII (Contd.)

INDIVIDUAL ANIMAL - OPHTHALMOSCOPIC EXAMINATION

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male Day : 0

Gr. No.	Dose mg/kg	Animal No.	Ophthalmoscopic Finding
V	1000	73	No Abnormality Detected
		74	No Abnormality Detected
		75	No Abnormality Detected
		76	No Abnormality Detected
		77	No Abnormality Detected
		78	No Abnormality Detected
		79	No Abnormality Detected
		80	No Abnormality Detected
		81	No Abnormality Detected
		82	No Abnormality Detected
VI	1000 (Reversal)	93	No Abnormality Detected
		94	No Abnormality Detected
		95	No Abnormality Detected
		96	No Abnormality Detected
		97	No Abnormality Detected
		98	No Abnormality Detected

APPENDIX NO.VII (Contd.)

INDIVIDUAL ANIMAL - OPHTHALMOSCOPIC EXAMINATION

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female Day : 0

Gr. No.	Dose mg/kg	Animal No.	Ophthalmoscopic Finding
I	0	11	No Abnormality Detected
		12	No Abnormality Detected
		13	No Abnormality Detected
		14	No Abnormality Detected
		15	No Abnormality Detected
		16	No Abnormality Detected
		17	No Abnormality Detected
		18	No Abnormality Detected
		19	No Abnormality Detected
		20	No Abnormality Detected
II	0 (Reversal)	27	No Abnormality Detected
		28	No Abnormality Detected
		29	No Abnormality Detected
		30	No Abnormality Detected
		31	No Abnormality Detected
		32	No Abnormality Detected
III	250	43	No Abnormality Detected
		44	No Abnormality Detected
		45	No Abnormality Detected
		46	No Abnormality Detected
		47	No Abnormality Detected
		48	No Abnormality Detected
		49	No Abnormality Detected
		50	No Abnormality Detected
		51	No Abnormality Detected
		52	No Abnormality Detected
IV	500	63	No Abnormality Detected
		64	No Abnormality Detected
		65	No Abnormality Detected
		66	No Abnormality Detected
		67	No Abnormality Detected
		68	No Abnormality Detected
		69	No Abnormality Detected
		70	No Abnormality Detected
		71	No Abnormality Detected
		72	No Abnormality Detected

APPENDIX NO.VII (Contd.)

INDIVIDUAL ANIMAL - OPHTHALMOSCOPIC EXAMINATION

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female Day : 0

Gr. No.	Dose mg/kg	Animal No.	Ophthalmoscopic Finding
V	1000	83	No Abnormality Detected
		84	No Abnormality Detected
		85	No Abnormality Detected
		86	No Abnormality Detected
		87	No Abnormality Detected
		88	No Abnormality Detected
		89	No Abnormality Detected
		90	No Abnormality Detected
		91	No Abnormality Detected
		92	No Abnormality Detected
VI	1000 (Reversal)	99	No Abnormality Detected
		100	No Abnormality Detected
		101	No Abnormality Detected
		102	No Abnormality Detected
		103	No Abnormality Detected
		104	No Abnormality Detected

APPENDIX NO.VII (Contd.)

INDIVIDUAL ANIMAL - OPHTHALMOSCOPIC EXAMINATION

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male Day : 90 and 118

Gr. No.	Dose mg/kg	Animal No.	Ophthalmoscopic Finding
I	0	1	No Abnormality Detected
		2	No Abnormality Detected
		3	No Abnormality Detected
		4	No Abnormality Detected
		5	No Abnormality Detected
		6	No Abnormality Detected
		7	No Abnormality Detected
		8	No Abnormality Detected
		9	No Abnormality Detected
		10	No Abnormality Detected
II	0 (Reversal)	21	No Abnormality Detected
		22	No Abnormality Detected
		23	No Abnormality Detected
		24	No Abnormality Detected
		25	No Abnormality Detected
		26	No Abnormality Deteeted
III	250	33	No Abnormality Detected
		34	No Abnormality Detected
		35	No Abnormality Detected
		36	No Abnormality Detected
		37	No Abnormality Detected
		38	No Abnormality Detected
		39	No Abnormality Detected
		40	No Abnormality Detected
		41	No Abnormality Detected
		42	No Abnormality Detected
IV	500	53	No Abnormality Detected
		54	No Abnormality Detected
		55	No Abnormality Detected
		56	No Abnormality Detected
		57	No Abnormality Detected
		58	No Abnormality Detected
		59	No Abnormality Detected
		60	No Abnormality Detected
		61	No Abnormality Detected
		62	No Abnormality Detected

APPENDIX NO.VII (Contd.)

INDIVIDUAL ANIMAL - OPHTHALMOSCOPIC EXAMINATION

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male Day : 90 and 118

Gr. No.	Dose mg/kg	Animal No.	Ophthalmoscopic Finding
V	1000	73	No Abnormality Detected
		74	No Abnormality Detected
		75	No Abnormality Detected
		76	No Abnormality Detected
		77	No Abnormality Detected
		78	No Abnormality Detected
		79	No Abnormality Detected
		80	No Abnormality Detected
		81	No Abnormality Detected
		82	No Abnormality Detected
VI	1000 (Reversal)	93	No Abnormality Detected
		94	No Abnormality Detected
		95	No Abnormality Detected
		96	No Abnormality Detected
		97	No Abnormality Detected
		98	No Abnormality Detected

APPENDIX NO.VII (Contd.)

INDIVIDUAL ANIMAL - OPHTHALMOSCOPIC EXAMINATION

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female Day : 90 and 118

Gr. No.	Dose mg/kg	Animal No.	Ophthalmoscopic Finding
I	0	11	No Abnormality Detected
		12	No Abnormality Detected
		13	No Abnormality Detected
		14	No Abnormality Detected
		15	No Abnormality Detected
		16	No Abnormality Detected
		17	No Abnormality Detected
		18	No Abnormality Detected
		19	No Abnormality Detected
		20	No Abnormality Detected
II	0 (Reversal)	27	No Abnormality Detected
		28	No Abnormality Detected
		29	No Abnormality Detected
		30	No Abnormality Detected
		31	No Abnormality Detected
		32	No Abnormality Detected
III	250	43	No Abnormality Detected
		44	No Abnormality Detected
		45	No Abnormality Detected
		46	No Abnormality Detected
		47	No Abnormality Detected
		48	No Abnormality Detected
		49	No Abnormality Detected
		50	No Abnormality Detected
		51	No Abnormality Detected
		52	No Abnormality Detected
IV	500	63	No Abnormality Detected
		64	No Abnormality Detected
		65	No Abnormality Detected
		66	No Abnormality Detected
		67	No Abnormality Detected
		68	No Abnormality Detected
		69	No Abnormality Detected
		70	No Abnormality Detected
		71	No Abnormality Detected
		72	No Abnormality Detected

APPENDIX NO.VII (Contd.)

INDIVIDUAL ANIMAL - OPHTHALMOSCOPIC EXAMINATION

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female Day : 90 and 118

Gr. No.	Dose mg/kg	Animal No.	Ophthalmoscopic Finding
V	1000	83	No Abnormality Detected
		84	No Abnormality Detected
		85	No Abnormality Detected
		86	No Abnormality Detected
		87	No Abnormality Detected
		88	No Abnormality Detected
		89	No Abnormality Detected
		90	No Abnormality Detected
		91	No Abnormality Detected
		92	No Abnormality Detected
VI	1000 (Reversal)	99	No Abnormality Detected
		100	No Abnormality Detected
		101	No Abnormality Detected
		102	No Abnormality Detected
		103	No Abnormality Detected
		104	No Abnormality Detected

APPENDIX NO.VIII

INDIVIDUAL ANIMAL - CLINICAL OBSERVATIONS AND GENERAL APPEARANCE

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number	Dose mg/kg	Animal Number	Observed Signs	Period of signs in days from - to
I	0	1	Nil	1 - 90
		2	Nil	1 - 90
		3	Nil	1 - 90
		4	Nil	1 - 90
		5	Nil	1 - 90
		6	Nil	1 - 90
		7	Nil	1 - 90
		8	Nil	1 - 90
		9	Nil	1 - 90
		10	Nil	1 - 90
II	0 (Reversal)	21	Nil	1 - 118
		22	Nil	1 - 118
		23	Nil	1 - 118
		24	Nil	1 - 118
		25	Nil	1 - 118
		26	Nil	1 - 118
III	250	33	Nil	1 - 90
		34	Nil	1 - 90
		35	Nil	1 - 90
		36	Nil	1 - 90
		37	Nil	1 - 90
		38	Nil	1 - 90
		39	Nil	1 - 90
		40	Nil	1 - 90
		41	Nil	1 - 90
		42	Nil	1 - 90

APPENDIX NO.VIII (Contd.)

INDIVIDUAL ANIMAL - CLINICAL OBSERVATIONS AND GENERAL APPEARANCE

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Male

Group Number	Dose mg/kg	Animal Number	Observed Signs	Period of signs in days from - to
IV	500	53	Nil	1 - 90
		54	Nil	1 - 90
		55	Nil	1 - 90
		56	Nil	1 - 90
		57	Nil	1 - 90
		58	Nil	1 - 90
		59	Nil	1 - 90
		60	Nil	1 - 90
		61	Nil	1 - 90
		62	Nil	1 - 90
V	1000	73	Nil	1 - 90
		74	Nil	1 - 90
		75	Nil	1 - 90
		76	Nil	1 - 90
		77	Nil	1 - 90
		78	Nil	1 - 90
		79	Nil	1 - 90
		80	Nil	1 - 90
		81	Nil	1 - 90
		82	Nil	1 - 90
VI	1000 (Reversal)	93	Nil	1 - 118
		94	Nil	1 - 118
		95	Nil	1 - 118
		96	Nil	1 - 118
		97	Nil	1 - 118
		98	Nil	1 - 118

APPENDIX NO.VIII (Contd.)

INDIVIDUAL ANIMAL - CLINICAL OBSERVATIONS AND GENERAL APPEARANCE

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number	Dose mg/kg	Animal Number	Observed Signs	Period of signs in days from - to
I	0	11	Nil	1 - 90
		12	Nil	1 - 90
		13	Nil	1 - 90
		14	Nil	1 - 90
		15	Nil	1 - 90
		16	Nil	1 - 90
		17	Nil	1 - 90
		18	Nil	1 - 90
		19	Nil	1 - 90
		20	Nil	1 - 90
II	0 (Reversal)	27	Nil	1 - 118
		28	Nil	1 - 118
		29	Nil	1 - 118
		30	Nil	1 - 118
		31	Nil	1 - 118
		32	Nil	1 - 118
III	250	43	Nil	1 - 90
		44	Nil	1 - 90
		45	Nil	1 - 90
		46	Nil	1 - 90
		47	Nil	1 - 90
		48	Nil	1 - 90
		49	Nil	1 - 90
		50	Nil	1 - 90
		51	Nil	1 - 90
		52	Nil	1 - 90

APPENDIX NO.VIII (Contd.)

INDIVIDUAL ANIMAL - CLINICAL OBSERVATIONS AND GENERAL APPEARANCE

Laboratory Test Item Code : TAS/002/015
Test System : Sprague Dawley Rat

Sex : Female

Group Number	Dose mg/kg	Animal Number	Observed Signs	Period of signs in days from - to
IV	500	63	Nil	1 - 90
		64	Nil	1 - 90
		65	Nil	1 - 90
		66	Nil	1 - 90
		67	Nil	1 - 90
		68	Nil	1 - 90
		69	Nil	1 - 90
		70	Nil	1 - 90
		71	Nil	1 - 90
		72	Nil	1 - 90
V	1000	83	Nil	1 - 90
		84	Nil	1 - 90
		85	Nil	1 - 90
		86	Nil	1 - 90
		87	Nil	1 - 90
		88	Nil	1 - 90
		89	Nil	1 - 90
		90	Nil	1 - 90
		91	Nil	1 - 90
		92	Nil	1 - 90
VI	1000 (Reversal)	99	Nil	1 - 118
		100	Nil	1 - 118
		101	Nil	I - 118
		102	Nil	1 - 118
		103	Nil	1 - 118
		104	Nil	1 - 118