Key to Tables 5 and 6 - Methods of detailed clinical observations, parameters, and scoring criteria

Handling

Parameters	Scoring criteria
Muscle tone	-2: Marked decrease -1: Slight decrease 0: Normal tone 1: Slight increase 2: Marked increase

Open field

Parameters	Scoring criteria	Parameters	Scoring criteria
Stereotypes	0: No abnormalities 1: Intermittent 2: Frequent 3: Continuous	Skin color	-2: Markedly pale -1: Slightly pale 0: Normal color 1: Slightly reddish 2: Markedly reddish
Exploration	-2: No exploration -1: Decrease 0: Intermittent 1: Frequent 2: Continuous	Rearing	Counts / 30 seconds
Count of defecation	Counts / 30 seconds	Defecation	0: Normal feces 1: Soft feces 2: Mucous feces 3: Diarrhea N: No defecation
Urination	0: Normal feces 1: Discolored urine 2: Colored urine 3: Polyuria N: No defecation		

Animals showed score 'N' were eliminated from the statistical evaluation.

Remarks:

Week -1, Before initiation of treatment.

Table 5 - 1 Detailed clinical observations - Summary data in male rats

Handling: Muscle tone

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
8	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	9	10	10
	1	0	0	1	0	0
	2	0	0	0	0	0
40	-2	0	0	0	0	0
	-1	0	0	1	0	1
	0	10	10	9	10	9
	1	0	0	0	0	0
	2	0	0	0	0	0
80	-2	0	0	0	0	0
	-1	0	3	3	2	2
	0	10	6	6	7	7
	1	0	0	0	0	0
	2	0	0 *	0	0	0

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

Table 5 - 2 Detailed clinical observations - Summary data in male rats

Open field: Stereotypes

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
8	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
40	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
80	0	10	9	9	9	9
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0

Table 5 - 3 Detailed clinical observations - Summary data in male rats

Open field: Skin color

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
8	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
40	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
80	-2	0	0	0	0	0
	-1	0	0	0	1	0
	0	10	9	9	8	9
	1	0	0	0	0	0
	2	0	0	0	0	0

Table 5 - 4 Detailed clinical observations - Summary data in male rats

Open field: Exploration

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	-2	0	0	0	0	0
	-1	0	0	2	1	1
	0	3	8	6	9	8
	1	7	2	2	0	1
	2	0	0	0	0	0
8	-2	0	0	0	0	0
	-1	0	1	1	1	1
	0	5	6	8	6	9
	1	5	3	1	3	0
	2	0	0	0	0	0
40	-2	0	0	0	0	0
	-1	0	3	6	6	4
	0	8	7	4	4	6
	1	2	0	0	0	0
	2	0	0	0	0	0
80	-2	0	0	0	0	1
	-1	0	2	7	7	3
	0	6	7	2	2	5
	1	4	0	0	0	0
	2	0	0	0	0	0
				*	*	

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

Table 5 - 5 Detailed clinical observations - Summary data in male rats

Open field: Rearing

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	0	0	5	4	6	3
	1	1	1	3	1	1
	2	0	3	0	2	4
	3	2	0	0	1	1
	4	1	0	1	0	1
	5	2	0	1	0	0
	6	3	1	1	0	0
	7	1	0	0	0	0
	8	0	0	0	0	0
	9	0	0	0	0	0
	10	0	0	0	0	0
8	0	0	3	2	1	2
	1	1	2	2	2	3
	2	4	1	1	2	2
	3	1	3	1	3	1
	4	1	1	2	2	1
	5	1	0	1	0	1
	6	1	0	0	0	0
	7	0	0	0	0	0
	8	0	0	0	0	0
	9	1	0	0	0	0
	10	0	0	1	0	0
					*	
40	0	1	3	8	10	8
	1	0	5	2	0	2
	2	3	1	0	0	0
	3	1	1	0	0	0
	4	1	0	0	0	0
	5	2	0	0	0	0
	6	1	0	0	0	0
	7	0	0	0	0	0
	8	0	0	0	0	0
	9	0	0	0	0	0
	10	1	0	0	0	0
						*
80	0	1	6	4	7	8
	1	0	2	4	1	1
	2	0	1	1	1	0
	3	3	0	0	0	0
	4	5	0	0	0	0
	5	1	0	0	0	0
	6	0	0	0	0	0
	7	0	0	0	0	0
	8	0	0	0	0	0
	9	0	0	0	0	0
	10	0	0	0	0	0
						*

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

Table 5 - 6 Detailed clinical observations - Summary data in male rats

Open field: Count of defecation

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	0	9	10	9	9	9
	1	0	0	0	1	0
	2	1	0	1	0	1
8	0	10	10	10	9	10
	1	0	0	0	0	0
	2	0	0	0	1	0
40	0	9	9	8	8	9
	1	1	1	2	1	1
	2	0	0	0	1	0
80	0	10	8	8	7	6
	1	0	0	0	2	1
	2	0	1	1	0	2

Table 5 - 7 Detailed clinical observations - Summary data in male rats

Open field: Defecation

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	0	1	0	1	1	1
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	9	10	9	9	9
8	0	0	0	0	1	0
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	10	10	10	9	10
40	0	1	1	2	2	1
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	9	9	8	8	9
80	0	0	1	1	2	3
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	10	8	8	7	6

Table 5 - 8 Detailed clinical observations - Summary data in male rats

Open field: Urination

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	0	1	4	3	4	2
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	9	6	7	6	8
8	0	2	6	2	3	1
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	8	4	8	7	9
40	0	3	4	1	3	2
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	7	6	9	7	8
80	0	4	5	5	4	2
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	6	4	4	5	7

Table 6 - 1 Detailed clinical observations - Summary data in female rats

Handling: Muscle tone

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
8	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
40	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	9	10
	1	0	0	0	1	0
	2	0	0	0	0	0
80	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0

Table 6 - 2 Detailed clinical observations - Summary data in female rats

Open field: Stereotypes

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
8	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
40	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
80	0	10	10	9	10	10
	1	0	0	1	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0

Table 6 - 3 Detailed clinical observations - Summary data in female rats

Open field: Skin color

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
8	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
40	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
80	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0

Table 6 - 4 Detailed clinical observations - Summary data in female rats

Open field: Exploration

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	-2	0	0	0	0	0
	-1	0	0	0	0	0
	0	5	8	6	5	10
	1	5	2	4	5	0
	2	0	0	0	0	0
8	-2	0	0	0	0	0
	-1	0	0	0	1	1
	0	8	7	6	6	7
	1	2	3	4	3	2
	2	0	0	0	0	0
40	-2	0	0	0	0	0
	-1	0	0	3	2	2
	0	8	9	6	8	8
	1	2	1	1	0	0
	2	0	0	0	0	0
80	-2	0	0	0	1	1
	-1	0	2	7	6	5
	0	7	7	3	3	4
	1	3	1	0	0	0
	2	0	0	0	0	0
				**	**	*

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

Table 6 - 5 Detailed clinical observations - Summary data in female rats

Open field: Rearing

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	0	0	0	0	0	0
	1	1	2	1	1	1
	2	1	4	3	2	0
	3	2	0	3	1	3
	4	2	2	0	3	3
	5	0	0	0	0	1
	6	1	1	1	1	0
	7	1	0	1	1	1
	8	1	0	0	0	1
	9	1	0	1	1	0
	10	0	1	0	0	0
8	0	1	3	0	1	1
	1	0	1	1	1	0
	2	1	1	2	1	2
	3	1	2	1	1	4
	4	1	0	1	3	2
	5	2	2	3	2	1
	6	3	0	0	1	0
	7	0	1	1	0	0
	8	1	0	1	0	0
	9	0	0	0	0	0
	10	0	0	0	0	0
40	0	0	1	4	1	1
	1	1	3	2	4	4
	2	2	5	1	3	3
	3	0	0	1	1	1
	4	4	0	1	1	1
	5	2	0	1	0	0
	6	0	0	0	0	0
	7	1	1	0	0	0
	8	0	0	0	0	0
	9	0	0	0	0	0
	10	0	0	0	0	0
						*
80	0	0	3	3	4	5
	1	0	4	5	6	4
	2	2	1	2	0	0
	3	1	2	0	0	1
	4	2	0	0	0	0
	5	2	0	0	0	0
	6	2	0	0	0	0
	7	0	0	0	0	0
	8	1	0	0	0	0
	9	0	0	0	0	0
	10	0	0	0	0	0
				**	**	**

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

Table 6 - 6 Detailed clinical observations - Summary data in female rats

Open field: Count of defecation

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	0	10	9	9	10	10
	1	0	1	1	0	0
	2	0	0	0	0	0
8	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0
40	0	10	9	10	10	9
	1	0	1	0	0	0
	2	0	0	0	0	1
80	0	10	10	10	10	10
	1	0	0	0	0	0
	2	0	0	0	0	0

Table 6 - 7 Detailed clinical observations - Summary data in female rats

Open field: Defecation

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	0	0	1	1	0	0
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	10	9	9	10	10
8	0	0	0	0	0	0
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	10	10	10	10	10
40	0	0	1	0	0	1
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	10	9	10	10	9
80	0	0	0	0	0	0
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	10	10	10	10	10

Table 6 - 8 Detailed clinical observations - Summary data in female rats

Open field: Urination

Dose (mg/kg/day)	Score	Week -1	1	2	3	4
0	0	0	5	1	0	0
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	10	5	9	10	10
8	0	0	1	0	1	2
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	10	9	10	9	8
40	0	0	2	0	0	0
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	10	8	10	10	10
80	0	0	2	1	0	1
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0
	N	10	8	9	10	9

Key to Tables 7 and 8

Standard key to functional observation data

Parameters assessed and scoring criteria of sensorimotor responses in the functional observation are described as follows:

In principle, the normal condition is defined as score 0.

Sensorimotor responses

Parameters	Scoring criteria
Visual placing	0: Normal response 1: Slight decrease 2: Marked decrease
Approach response	-2: Marked decrease -1: Slight decrease 0: Normal response 1: Slight increase 2: Marked increase
Auditory response	-2: Marked decrease -1: Slight decrease 0: Normal response 1: Slight increase 2: Marked increase
Touch response	-2: Marked decrease -1: Slight decrease 0: Normal response 1: Slight increase 2: Marked increase
Pain response	-2: Marked decrease -1: Slight decrease 0: Normal response 1: Slight increase 2: Marked increase
Aerial righting reflex	0: Normal reflex 1: Slight decrease 2: Marked decrease 3: No reflex

Table 7 - 1 Functional observation - Summary data in male rats

Motor activity at 4 weeks of treatment

Dose (mg/kg)	No.of animals examined		Counts/10 min						Total
			0-10	10-20	20-30	30-40	40-50	50-60	
0	10	Mean	1682	1006	417	243	193	210	3751
		S.D.	265	481	468	258	338	287	1460
8	10	Mean	1423	898	508	271	65	110	3275
		S.D.	263	486	253	372	80	169	1067
40	10	Mean	1363 *	843	275	133	167	104	2885
		S.D.	281	431	212	256	266	283	1254
80	9	Mean	1161 **	748	546	347	403	201	3404
		S.D.	304	364	405	336	373	196	1258

S.D.: Standard deviation.

Table 7 - 2 Functional observation - Summary data in male rats

Grip strength at 4 weeks of treatment (g)

Dose (mg/kg)	No.of animals examined		Forelimb	Hindlimb
0	10	Mean	642	333
		S.D.	102	34
8	10	Mean	642	337
		S.D.	61	36
40	10	Mean	635	337
		S.D.	87	45
80	9	Mean	632	335
		S.D.	80	20

S.D.: Standard deviation.