

**HISTORICAL CONTROL DATA FROM PRE- AND POSTNATAL
DEVELOPMENTAL TOXICITY STUDIES
IN HsdRccHanTM : WIST, Wistar Hannover Rats**

**Compiled from pre- and postnatal Developmental toxicity studies
performed at RCC Ltd. Itingen/Switzerland**

Contents: Sperm analysis

Table 1: Study identification	3
Table 2: Breeding Data per Group - F0 Generation	4
Table 3: External Examination of F1 Pups at First Litter Check after Parturition	5
Table 4: Mean Body Weights of Pups per Group (gram) - F1 pups	6
Table 5: Developmental Indices per Group (Days Post Partum) - F1 pups	7
Table 6: Reproduction data - F1 generation	8
Appendix: Statistics	9

Historical control data from pre- and postnatal developmental toxicity studies in HsdRccHanTM : WIST, Wistar Hannover Rats

Table 1: Study Identification

Study ID	Number of study	Date of performance
1	798118	Oct 2001
2	853347	Jul-04
3	853804	Aug-04
4	855739	Jan-05

Table 2: Breeding Data per Group - F0 Generation

Parameter	1	2	3	4
Number of Females Mated	22	22	12	20
Pregnant	22	20	11	20
Used for Calculation	22	20	11	20
Duration of Gestation				
Mean	21.4	21.5	21.5	21.6
Implantation				
Total	268	264	145	284
Mean	12.2	13.2	13.2	14.2
Post Implantation Loss				
% of Implantations	6	2.7	5.5	6.3
Litters Affected	13	5	6	12
Total	16	7	8	18
Mean	0.7	0.4	0.7	0.9
Dead Pups at first Litter Check				
Litters Affected	0	0	0	0
Total	0	0	0	0
Mean	0	0	0	0
Living Pups at first Litter Check				
% of Males / Females	49 / 51	49 / 51	47 / 53	46 / 54
Total	252	257	137	266
Mean	11.5	12.9	12.5	13.3
Postnatal Loss Days 0-4 P.P				
% of living Pups	0.8	1.2	3.6	3.8
Litters Affected	2	3	3	9
Total	2	3	5	10
Mean	0.1	0.2	0.5	0.5

Table 2: Breeding Data per Group - F0 Generation Cont'd

Parameter	1	2	3	4
Living Pups Day 4 P.P.				
Total	250	254	85	160
Mean	11.4	12.7	7.7	8
Breeding Loss Days 5-21 P.P.				
% of Living Pups at Dayv4 P.P.	1.6	1.2	11.8	2.5
Litters Affected	3	3	6	3
Total	4	3	10	4
Mean	0.2	0.2	0.9	0.2
Living Pups Day P.P.				
% of Males / Females	50 / 50	49 / 51	55 / 45	49 / 51
Total	246	251	75	156
Mean	11.2	12.6	6.8	7.8
Birth Index	94	97.3	94.5	93.7
Viability Index	99.2	98.8	96.4	96.2
Weaning Index	98.4	98.8	88.2	97.5

Table 3: External Examination of F1 Pups at First Litter Check After Parturition

Parameter	Vehicle Control Group							
	1		2		3		4	
Number of Litters / Pups	22 / 252		20 / 257		11 / 137		20 / 156	
Abnormal Findings	Number		Number		Number		Number	
	Pups	Litters	Pups	Litters	Pups	Litters	Pups	Litters
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Oral Region with Hemorrhage, Abdomen, Contents Appeared Dark	0	0	0	0	0	0	1 (1.6)	1 (0.2)

Table 4: MEAN BODY WEIGHTS OF PUPS PER GROUP (GRAM) - F1 PUPS

PARAMETER			Vehicle Control Group			
			1	2	3	4
Day	Sex					
1	M	mean	6.2	6.4	6.4	6.4
		n (litter)	22	20	11	20
	F	mean	5.9	6.2	6.1	5.9
		n (litter)	22	20	11	20
	M + F	mean	6.1	6.3	6.3	6.1
		n (litter)	22	20	11	20
4	M	mean	8.9	9.8	9.4	9
		n (litter)	22	20	11	20
	F	mean	8.5	9.4	9	8.6
		n (litter)	22	20	11	20
	M + F	mean	8.7	9.6	9.2	8.8
		n (litter)	22	20	11	20
7	M	mean	12.8	14.2	15.4	14.6
		n (litter)	22	20	11	20
	F	mean	12.3	13.7	14.8	14.1
		n (litter)	22	20	11	20
	M + F	mean	12.6	14	15.1	14.3
		n (litter)	22	20	11	20
14	M	mean	25.2	26.4	33	31.2
		n (litter)	22	20	11	20
	F	mean	24.5	25.5	32.1	30.7
		n (litter)	22	20	11	20
	M + F	mean	24.9	25.9	32.6	30.9
		n (litter)	22	20	11	20

Table 4: Mean Body weights of Pups per Group (Gram)-F1 Pups. Cont'd

Parameter			Vehicle Control Group			
			1	2	3	4
DAY	SEX					
21	M	mean	39.7	41	52.7	49.9
		n (litter)	22	20	11	20
	F	mean	38.9	39.7	51.2	48.5
		n (litter)	22	20	11	20
	M + F	mean	39.4	40.4	52	49.1
		n (litter)	22	20	11	20

Table 5: Developmental Indices per Group (Days Post Partum) - F1 Pups

Parameter		2	3	4
Pinna Unfolding	mean	3.3	3	3.8
	n	22	20	11
Incisor Eruption	mean	7.3	7	7.5
	n	22	20	11
Onset of Coat Development	mean	10.1	10.1	10
	n	22	20	11
Opening of Eye	mean	14.8	14.5	14.5
	n	22	20	11
Descensus of Testes	mean	22.8	22.4	21.5
	n	22	20	11
Opening of Prepuce	mean	28.2	-	-
	n	22	-	-
Balano - Preputial Sep	mean		26.6	-
	n		20	-
Opening of Vagina	mean	32.2	32.9	-
	n	22	20	-

Table 6: Reproduction Data - F1 Generation

Parameter	CONTROLS	
	1	2
Number of Dams	22	22
Corpora Lutea	276	292
Mean	13.1	13.3
ST. DEV.	2.1	1.6
Pre-Implantation Loss	11	15
% of Coropora Lutea	4	5.1
Mean	0.5	0.7
ST. DEV.	1	1.5
Number of Dams Affected	6	7
Implantation Sites	265	277
% of Coropora Lutea	96	94.9
Mean	12.6	12.6
ST. DEV.	1.8	2
Post Implantation Loss	22	17
% of Implantation Sites	8.3	6.1
Mean	1	0.8
ST. DEV.	1.1	1
Number of Dams Affected	13	11
Implantation Site Scars	0	0
Embryonic / Fetal Deatgs Total	22	
Embryonic Resorptions	22	17
Fetal Resorptions	0	

Table 6: Reproduction Data - F1 Generation. Cont'd

Parameter	CONTROLS	
	1	2
Live Fetuses	243	260
Dead Fetuses	0	0
Abonormal Fetuses	0	0

Contents Statistics:

Table 1: Statistic Breeding Data per Group - F0 Generation	10
Table 2: Mean Body weights of Pups per Group (Gram) - F1 Pups	11
Table 3: Developmental IndicesPer Grooup (Days Post Partum) - F1 Pups	12
Table 4: Reproduction Data - F1 Generation	13

Table 1: Statistic Breeding Data per Group - F0 Generation

	Total n	Mean	STDE V	MIN	MAX
Number of Females Mated	76	19.00	4.76	12.00	22.00
Pregnant	73	18.25	4.92	11.00	22.00
Used for Calculation	73	18.25	4.92	11.00	22.00
Duration of Gestation					
Mean	86	21.50	0.08	21.40	21.60
ST. DEV.	2	0.51	0.01	0.50	0.52
Implantations					
Total	961	240.25	64.09	145.00	284.00
Mean	53	13.20	0.82	12.20	14.20
ST. DEV.	8	2.12	0.74	1.15	2.82
Post Implantation Loss					
% of Implantations	21	5.13	1.65	2.70	6.30
Litters Affected	36	9.00	4.08	5.00	13.00
Total	49	12.25	5.56	7.00	18.00
Mean	3	0.68	0.21	0.40	0.90
ST. DEV.	3	0.80	0.16	0.67	1.02
Dead Pups at first Litter Check					
Litters Affected	0	0.00	0.00	0.00	0.00
Total	0	0.00	0.00	0.00	0.00
Mean	0	0.00	0.00	0.00	0.00
ST. DEV.	0	0.00	0.00	0.00	0.00
Living Pups at first Litter Check					
% of Males / Females					
Total	912	228.00	60.94	137.00	266.00
Mean	50	12.55	0.77	11.50	13.30
ST. DEV.	10	2.41	0.79	1.38	3.17
Postnatal Loss Days 0 - 4 P.P.					
% of Living Pups	9	2.35	1.57	0.80	3.80
Litters Affected	17	4.25	3.20	2.00	9.00
Total	20	5.00	3.56	2.00	10.00
Mean	1	0.33	0.21	0.10	0.50
ST. DEV.	2	0.52	0.24	0.29	0.82

Table 1: Statistic Breeding Data per Group - F0 Generation. Cont'd

	Total n	Mean	STDE V	MIN	MAX
Living Pups Day 4 P.P.					
Total	749	187.25	80.81	85.00	254.00
Mean	40	9.95	2.49	7.70	12.70
ST. DEV.	6	1.43	1.34	0.00	2.92
Breeding Loss Days 5 - 21 P.P.					
% of Living Pups at Day 4 P.P.	17	4.28	5.05	1.20	11.80
Litters Affected	15	3.75	1.50	3.00	6.00
Total	21	5.25	3.20	3.00	10.00
Mean	2	0.38	0.35	0.20	0.90
ST. DEV.	3	0.65	0.38	0.37	1.22
Living Pups Day 21 P.P.					
% of Males / Females					
Total	728	182.00	83.63	75.00	251.00
Mean	38	9.60	2.75	6.80	12.60
ST. DEV.	7	1.84	0.99	0.52	2.86
Birth Index	380	94.88	1.65	93.70	97.30
Viability Index	391	97.65	1.57	96.20	99.20
Weaning Index	383	95.73	5.05	88.20	98.80

Table 2: Mean Body weights of Pups per Group (Gram) - F1 Pups

Parameter			Total n	Mean	STDE V	MIN	MAX
Day	Sex						
1	M	mean	25	6.35	0.10	6.20	6.40
		n (litter)	73	18.25	4.92	11.00	22.00
	F	mean	24	6.03	0.15	5.90	6.20
		n (litter)	73	18.25	4.92	11.00	22.00
	M + F	mean	25	6.20	0.12	6.10	6.30
		n (litter)	73	18.25	4.92	11.00	22.00
4	M	mean	37	9.28	0.41	8.90	9.80
		n (litter)	73	18.25	4.92	11.00	22.00
	F	mean	36	8.88	0.41	8.50	9.40
		n (litter)	73	18.25	4.92	11.00	22.00
	M + F	mean	36	9.08	0.41	8.70	9.60
		n (litter)	73	18.25	4.92	11.00	22.00
7	M	mean	57	14.25	1.09	12.80	15.40
		n (litter)	73	18.25	4.92	11.00	22.00
	F	mean	55	13.73	1.05	12.30	14.80
		n (litter)	73	18.25	4.92	11.00	22.00
	M + F	mean	56	14.00	1.04	12.60	15.10
		n (litter)	73	18.25	4.92	11.00	22.00
14	M	mean	116	28.95	3.74	25.20	33.00
		n (litter)	73	18.25	4.92	11.00	22.00
	F	mean	88	29.43	3.48	25.50	32.10
		n (litter)	73	18.25	4.92	11.00	22.00
	M + F	mean	94	23.58	7.77	12.60	30.90
		n (litter)	73	18.25	4.92	11.00	22.00

Table 2: Mean Body weights of Pups per Group (Gram) - F1 Pups. Cont'd

Parameter			Total n	Mean	STDE V	MIN	MAX
Day	Sex						
21	M	mean	183	45.83	6.45	39.70	52.70
		n (litter)	73	18.25	4.92	11.00	22.00
	F	mean	178	44.58	6.20	38.90	51.20
		n (litter)	73	18.25	4.92	11.00	22.00
	M + F	mean	181	45.23	6.28	39.40	52.00
		n (litter)	73	18.25	4.92	11.00	22.00

Table 3: Developmental Indices Per Group (Days Post Partum) - F1 Pups

Parameter		Total n	Mean	STDE V	MIN	MAX
Pinna Unfolding	mean	10	3.37	0.40	3.00	3.80
	n (litter)	53	17.67	5.86	11.00	22.00
Incisor Eruption	mean	22	7.27	0.25	7.00	7.50
	n (litter)	53	17.67	5.86	11.00	22.00
Onset of Coat Development	mean	30	10.07	0.06	10.00	10.10
	n (litter)	53	17.67	5.86	11.00	22.00
Opening of Eye	mean	44	14.60	0.17	14.50	14.80
	n (litter)	53	17.67	5.86	11.00	22.00
Descensus of Testes	mean	67	22.23	0.67	21.50	22.80
	n (litter)	53	17.67	5.86	11.00	22.00
Opening of Prepuce	mean	28	28.20		28.20	28.20
	n (litter)	22	22.00		22.00	22.00
Balano - Preputial Sep	mean	27	26.60		26.60	26.60
	n (litter)	20	20.00		20.00	20.00
Opening of Vagina	mean	65	32.55	0.49	32.20	32.90
	n	42	21.00	1.41	20.00	22.00

Table 4: Reproduction Data - F1 Generation

Parameter	Total n	Mean	STDE V	MIN	MAX
Number of Dams	44	22.00	0.00	22.00	22.00
Corpora Lutea	568	284.00	11.31	276.00	292.00
Mean	26	13.20	0.14	13.10	13.30
ST. DEV.	4	1.85	0.35	1.60	2.10
Pre-Implantation Loss	26	13.00	2.83	11.00	15.00
% of Corpora Lutea	9	4.55	0.78	4.00	5.10
Mean	1	0.60	0.14	0.50	0.70
ST. DEV.	3	1.25	0.35	1.00	1.50
Number of dams Affected	13	6.50	0.71	6.00	7.00
Implantation Sites	542	271.00	8.49	265.00	277.00
% of Corpora Lutea	191	95.45	0.78	94.90	96.00
Mean	25	12.60	0.00	12.60	12.60
ST. DEV.	4	1.90	0.14	1.80	2.00
Post Implantation Loss	39	19.50	3.54	17.00	22.00
% of implantation Sites	14	7.20	1.56	6.10	8.30
Mean	2	0.90	0.14	0.80	1.00
ST. DEV.	2	1.05	0.07	1.00	1.10
Number of dams Affected	24	12.00	1.41	11.00	13.00
Implantation Site Scars	0	0.00	0.00	0.00	0.00
Embryonic / Fetal Deats Total	22	22.00		22.00	22.00
Embryonic Resorptions	39	19.50	3.54	17.00	22.00
Fetal Resorptions	0	0.00		0.00	0.00

Table 4: Reproduction Data - F1 Generation. Cont'd

Parameter	Total n	Mean	STDE V	MIN	MAX
Live Fetuses	503	251.50	12.02	243.00	260.00
Dead Fetuses	0	0.00	0.00	0.00	0.00
Abnormal Fetuses	0	0.00	0.00	0.00	0.00