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[redacted]

Appendix A: Raw and summarised data

[redacted]

Table A1: In-life-data: of male test animals (body weight, food & water consumption, grip strength and beam walking score)

Group/Application		Food [g]					Water [g]										Body weight [g]					% init Body weight					GS [g]	Rel. GS	BWS	
Males		Thu 1 24.11.	Thu 8 01.12.	Thu 15 08.12.	Thu 22 15.12.	Thu 29 22.12.	Thu 1 24.11.	Sun 4 27.11.	Thu 8 01.12.	Sun 11 04.12.	Thu 15 08.12.	Sun 18 11.12.	Thu 22 15.12.	Sun 25 18.12.	Thu 29 22.12.	Animal#	Thu 1 24.11.	Thu 8 01.12.	Thu 15 08.12.	Thu 22 15.12.	Thu 29 22.12.	Day 1	Day 8	Day 15	Day 22	Day 29	Day 22	Day 22	Score	Time
High dose [redacted]	old	0	1000	923	1008	1044	0	1393	549	1489	1240	1076	1042	1120	1075	0	243	276	295	316	336	100	114	121	130	138	934	296	7	22
	new	1785	1734	1810	1850		1864	1393	2014	1985	1702	1831	1733	1845		1	236	264	278	299	312	100	112	118	127	132	572	191	7	9
	Difference		786	811	802	806		471	844	525	746	626	789	813	770	2	256	282	308	333	350	100	110	120	130	137	459	138	7	9
																3	235	260	284	296	304	100	111	121	126	129	256	86	7	23
			1-8	8-15	15-22	22-29		1-4	4-8	8-11	11-15	15-18	18-22	22-25	25-29	4	244	274	291	309	322	100	112	119	127	132	598	194	6	36
	Animal / Day		22,5	23,2	22,9	23,0		31,4	42,2	35,0	37,3	41,7	39,5	40,9	38,5	Mean	243	271	291	311	325	-	112	120	128	134	564	181	7	20
																SD	8,4	9,0	11,4	14,8	18,5	-	1,4	1,4	2,0	3,7	247	76	0	11
																ttest vs Veh p=	0,30 n.s.	0,82 n.s.	0,93 n.s.	0,85 n.s.	0,87 n.s.	0,000 0	0,14 n.s.	0,15 n.s.	0,20 n.s.	0,25 n.s.	0,72 n.s.	0,81 n.s.		
Medium dose E 792 [redacted]	old	0	1024	958	890	1009	0	1441	591	1495	1218	1066	1035	1110	1071	0	261	283	318	345	363	100	108	122	132	139	358	104	7	36
	new	1819	1773	1702	1822		1926	1441	2002	1924	1656	1795	1683	1789		1	250	279	291	315	321	100	112	116	126	128	437	139	6	18
	Difference		795	816	812	813		485	851	507	706	590	760	573	719	2	252	284	295	311	321	100	113	117	123	127	473	152	7	8
																3	246	270	290	307	314	100	110	118	125	128	579	189	7	15
			1-8	8-15	15-22	22-29		1-4	4-8	8-11	11-15	15-18	18-22	22-25	25-29	4	243	284	284	297	311	100	109	117	122	128	332	112	7	25
	Animal / Day		22,7	23,3	23,2	23,2		32,3	42,5	33,8	35,3	39,4	38,0	38,2	35,9	Mean	250	276	296	315	326	-	110	118	126	130	436	139	7	20
																SD	6,9	8,7	13,1	18,1	21,1	-	1,9	2,2	3,9	5,0	98,4	34	0	11
																ttest vs Veh p=	0,76 n.s.	0,71 n.s.	0,63 n.s.	0,63 n.s.	0,81 n.s.	0,000 0	0,70 n.s.	0,53 n.s.	0,56 n.s.	0,85 n.s.	0,29 n.s.	0,29 n.s.		
Low dose E 793 [redacted]	old	0	966	884	890	855	0	1478	633	1545	1304	1187	1101	1481	1010	0	249	280	305	320	342	100	112	122	129	137	616	193	7	13
	new	1770	1736	1730	1723		1929	1478	2010	1982	1728	1858	1991	1779		1	256	282	302	326	338	100	110	118	127	132	835	256	7	48
	Difference		804	852	840	868		451	845	465	678	540	757	510	770	2	236	263	285	306	322	100	111	121	130	136	820	268	6	90
																3	245	267	288	306	325	100	109	118	125	133	456	149	6	22
			1-8	8-15	15-22	22-29		1-4	4-8	8-11	11-15	15-18	18-22	22-25	25-29	4	241	263	280	302	320	100	109	116	125	133	699	231	7	32
	Animal / Day		23,0	24,3	24,0	24,8		30,1	42,3	31,0	33,9	36,0	37,9	34,0	38,5	Mean	245	271	292	312	329	-	110	119	127	134	685	219	7	41
																SD	7,6	9,3	10,9	10,4	9,9	-	1,5	2,6	2,0	2,5	157	49	1	30
																ttest vs Veh p=	0,53 n.s.	0,81 n.s.	0,87 n.s.	0,75 n.s.	0,60 n.s.	0,000 0	0,57 n.s.	0,32 n.s.	0,28 n.s.	0,18 n.s.	0,10 n.s.	0,17 n.s.		
Vehicle E 794 Water	old	0	1037	998	873	942	0	1443	669	1806	1385	1348	1108	1529	1195	0	253	275	292	310	326	100	109	115	123	129	349	113	7	8
	new	1836	1815	1696	1743		1864	1443	2003	1983	1771	1762	1985	1841		1	249	278	301	325	338	100	112	121	131	136	501	154	6	39
	Difference		800	817	823	801		441	774	396	599	423	654	456	646	2	246	271	279	293	309	100	110	113	119	126	679	232	6	17
																3	236	250	263	274	283	100	106	111	116	120	602	220	7	24
			1-8	8-15	15-22	22-29		1-4	4-8	8-11	11-15	15-18	18-22	22-25	25-29	4	260	291	316	338	355	100	112	122	130	137	454	134	7	12
	Animal / Day		22,8	23,3	23,5	22,9		29,4	38,7	26,4	29,9	28,2	32,7	30,4	32,3	Mean	249	273	290	308	322	-	110	117	124	129	517	171	7	20
																SD	8,9	14,9	20,3	25,4	27,6	-	2,5	4,5	6,5	7,0	128	53	1	12

n.s.: not significant. Asterisks denote significance levels: *: p < 0,05, **: p < 0,01, ***: p < 0,001

[redacted]

Table A2: In-life-data: of female test animals (body weight, food & water consumption, grip strength and beam walking score)

Group/Application		Food [g]					Water [g]									Animal#	Body weight [g]					% init Body weight					GS [g]	Rel. GS	BWS	
		Fri 1	Fri 8	Fri 15	Fri 22	Fri 29	Fri 1	Mon 4	Fri 8	Mon 11	Fri 15	Mon 18	Fri 22	Mon 25	Fri 29		Fri 1	Fri 8	Fri 15	Fri 22	Fri 29	Day 1	Day 8	Day 15	Day 22	Day 29	Day 22	Day 22	Score	Time
Females		25.11.	02.12.	09.12.	16.12.	23.12.	25.11.	28.11.	02.12.	05.12.	09.12.	12.12.	16.12.	19.12.	23.12.		25.11.	02.12.	09.12.	16.12.	23.12.									
High dose	old	0	1047	1031	1039	981	0	1410	602	1518	765	1373	1072	1122	1035	0	178	187	205	208	222	100	105	115	117	125	378	182	6	22
E 795	new	1720	1699	1731	1644		1905	1410	1978	1518	1888	1666	1624	1736		1	180	201	210	212	223	100	112	117	118	124	258	122	7	8
[redacted]	Difference		674	669	692	663		496	808	460	753	515	595	502	701	2	185	195	208	222	225	100	105	112	120	122	252	114	7	4
																3	187	200	214	219	232	100	107	114	117	124	359	164	6	26
			1-8	8-15	15-22	22-29		1-4	4-8	8-11	11-15	15-18	18-22	22-25	25-29	4	188	203	210	224	233	100	108	112	119	124	221	99	7	5
	Animal / Day		19,2	19,1	19,8	19,0		33,0	40,4	30,7	37,7	34,3	29,7	33,4	35,1	Mean	184	197	209	217	227	-	107	114	118	124	294	136	7	13
																SD	4,4	6,4	3,3	6,8	5,1	-	2,7	2,0	1,4	1,2	70	35	1	10
																ttest vs	0,82	0,56	0,76	0,96	0,49	0,000	0,37	0,86	0,77	0,01	0,43	0,47		
																Veh p=	n.s.	n.s.	n.s.	n.s.	n.s.	0	n.s.	n.s.	n.s.	*	n.s.	n.s.		
Med dose	old	0	1100	1061	1087	1095	0	1448	627	1565	822	1414	865	992	1243	0	182	200	208	215	225	100	110	114	118	124	225	105	7	13
E 796	new	1719	1674	1720	1682		1919	1448	1991	1565	1889	1563	1520	1822		1	180	197	206	212	221	100	109	114	118	123	182	86	7	10
[redacted]	Difference		618	613	633	586		471	821	426	744	475	698	529	578	2	179	193	203	205	209	100	108	113	115	117	348	170	7	8
																3	180	192	200	208	212	100	107	111	116	118	124	60	7	4
			1-8	8-15	15-22	22-29		1-4	4-8	8-11	11-15	15-18	18-22	22-25	25-29	4	190	203	214	214	225	100	107	113	113	118	127	59	7	9
	Animal / Day		17,7	19,8	22,6	20,9		31,4	41,0	28,4	37,2	31,7	34,9	35,2	36,2	Mean	182	197	206	211	218	-	108	113	116	120	201	96	7	9
																SD	4,5	4,6	5,3	4,2	7,5	-	1,5	1,4	2,3	3,1	92	46	0	3
																ttest vs	0,65	0,52	0,48	0,44	0,75	0,000	0,54	0,45	0,48	0,85	0,05	0,07		
																Veh p=	n.s.	n.s.	n.s.	n.s.	n.s.	0	n.s.	n.s.	n.s.	n.s.	*	n.s.		
Low dose	old	0	1115	1117	1166	1100	0	1403	624	1544	836	1482	884	1423	898	0	187	201	214	222	226	100	107	114	119	121	175	79	7	14
E 797	new	1741	1731	1798	1710		1897	1403	2007	1544	1978	1629	1932	1633		1	182	202	206	210	222	100	111	113	115	122	295	140	6	8
[redacted]	Difference		627	614	632	609		493	779	463	708	496	745	509	734	2	180	193	206	217	228	100	107	114	121	127	185	85	7	4
																3	190	209	220	222	237	100	110	116	117	125	371	167	6	9
			1-8	8-15	15-22	22-29		1-4	4-8	8-11	11-15	15-18	18-22	22-25	25-29	4	172	187	190	198	201	100	109	110	115	117	177	89	7	6
	Animal / Day		17,9	17,5	18,1	17,4		32,9	39,0	30,8	35,4	33,1	37,3	33,9	36,7	Mean	182	198	207	214	223	-	109	114	117	122	241	112	7	8
																SD	6,9	8,5	11,3	10,1	13,4	-	1,6	2,0	2,3	3,8	89	39	1	4
																ttest vs	0,67	0,69	0,62	0,70	0,87	0,000	0,99	0,68	0,94	0,22	0,13	0,15		
																Veh p=	n.s.	n.s.	n.s.	n.s.	n.s.	0	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.		
Vehicle	old	0	1180	1149	1153	1141	0	1530	912	1549	855	1578	1248	1329	1085	0	177	189	198	204	206	100	107	112	115	116	432	212	7	11
E 798	new	1793	1764	1793	1749		1925	1530	1958	1549	2010	1847	1807	1733		1	203	218	227	230	246	100	107	112	113	121	308	134	7	10
Water	Difference		613	615	640	608		395	618	408	695	432	600	478	649	2	174	193	201	207	213	100	111	116	119	122	406	196	7	15
																3	178	192	202	204	209	100	108	113	115	117	207	101	7	5
			1-8	8-15	15-22	22-29		1-4	4-8	8-11	11-15	15-18	18-22	22-25	25-29	4	193	215	230	242	232	100	111	119	125	120	325	134	6	38
	Animal / Day		17,5	17,6	18,3	17,4		26,3	30,9	27,2	34,7	28,8	30,0	31,9	32,4	Mean	185	201	212	217	221	-	109	114	118	120	336	156	7	16
																SD	12,5	13,9	15,5	17,5	17,2	-	2,1	3,1	4,9	2,5	89	47	0	13

n.s.: not significant. Asterisks denote significance levels: *: p < 0,05, **: p < 0,01, ***: p < 0,001

[redacted]

Table A3: Detailed clinical signs (IRWIN test), pre dose

DCS Irwin-Test

	Male																				Female																			
	E 791					E 792					E 793					E 794					E 795					E 796					E 797					E 798				
	High dose					Medium dose					Low dose					vehicle					High dose					Medium dose					Low dose					vehicle				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Appearence																																								
general status	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
physiologie/ autonomic functions	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
neurologie	12	12	12	12	12	12	12	12	12	12	12	12	13	12	12	12	12	12	12	13	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
tonus	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Motoric, Exploration																																								
motoric	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	6	6	6	6	6	6	6	6	6	6	6	6	6	6
exploration behaviour	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	5	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Exzitation																																								
exzitation	8	8	8	8	8	8	8	8	9	8	8	9	9	8	9	9	8	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Abnormal Behaviour																																								
freezing, tremor	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
stereotypies, abnormal movement	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
sel- mutilation	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
urine and faeces	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	52	52	52	52	52	52	52	52	53	52	52	53	54	52	53	53	52	53	53	53	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52

Table A4: Detailed clinical signs (IRWIN test), 1. week

DCS Irwin-Test

[redacted]

[redacted]	Male																			
	E 791					E 792					E 793					E 794				
	High dose					Medium dose					Low dose					vehicle				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Appearence																				
general status	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
physiologie/ autonomic functions	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
neurologie	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
tonus	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Motoric, Exploration																				
motoric	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
exploration behaviour	4	4	4	4	4	4	5	4	4	4	4	4	4	4	4	4	4	4	4	4
Exzitation																				
exzitation	8	8	8	8	8	8	7	8	8	8	8	8	8	8	8	8	8	8	8	8
Abnormal Behaviour																				
freezing, tremor	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
stereotypies, abnormal movement	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
sel- mutilation	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
urine and faeces	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52

[redacted]

[redacted]	Female																			
	E 795					E 796					E 797					E 798				
	High dose					Medium dose					Low dose					vehicle				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Appearence																				
general status	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
physiologie/ autonomic functions	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
neurologie	12	10	12	12	12	12	12	12	12	12	12	12	12	12	12	12	13	12	12	12
tonus	4	4	4	5	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Motoric, Exploration																				
motoric	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
exploration behaviour	4	4	4	5	4	4	4	4	4	4	4	4	4	4	5	4	4	5	5	5
Exzitation																				
exzitation	7	8	8	10	8	9	8	8	8	9	7	9	8	9	9	6	6	9	7	9
Abnormal Behaviour																				
freezing, tremor	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
stereotypies, abnormal movement	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
sel- mutilation	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
urine and faeces	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	51	50	52	56	52	53	52	52	52	53	51	53	52	53	54	50	51	54	52	54

[redacted]

Table A5: Detailed clinical signs (IRWIN test), 2. week

DCS Irwin-Test [redacted]

[redacted]	Male																			
	E 791					E 792					E 793					E 794				
	High dose					Medium dose					Low dose					vehicle				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Appearence																				
general status	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
physiologie/ autonomic functions	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
neurologie	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
tonus	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Motoric, Exploration																				
motoric	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
exploration behaviour	4	4	4	5	5	5	4	4	4	4	5	4	4	4	4	4	4	4	5	4
Exzitation																				
exzitation	8	8	7	7	8	8	8	8	8	8	7	8	7	7	8	8	8	8	8	7
Abnormal Behaviour																				
freezing, tremor	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
stereotypies, abnormal movement	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
sel- mutilation	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
urine and faeces	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	52	52	51	52	53	53	52	52	52	52	52	52	51	51	52	52	52	52	53	51

[redacted]	Female																			
	E 795					E 796					E 797					E 798				
	High dose					Medium dose					Low dose					vehicle				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Appearence																				
general status	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
physiologie/ autonomic functions	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
neurologie	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
tonus	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Motoric, Exploration																				
motoric	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
exploration behaviour	4	4	4	4	4	4	4	4	4	4	5	4	4	4	4	4	4	5	4	5
Exzitation																				
exzitation	8	8	8	8	8	8	7	8	8	8	7	7	8	8	8	8	7	8	8	8
Abnormal Behaviour																				
freezing, tremor	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
stereotypies, abnormal movement	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
sel- mutilation	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
urine and faeces	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	52	52	52	52	52	52	51	52	52	52	52	51	52	52	52	52	51	53	52	53

Table A6: Detailed clinical signs (IRWIN test), 3. week

DCS Irwin-Test

[redacted]	Male																				Female																									
	E 791					E 792					E 793					E 794					E 795					E 796					E 797					E 798				
	High dose					Medium dose					Low dose					vehicle					High dose					Medium dose					Low dose					vehicle				
[redacted]	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Appearence																																												
general status	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
physiologie/ autonomic functions	10	10	10	10	10	10	10	10	10	10	10	10	9	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
neurologie	12	12	12	12	12	13	13	12	13	13	13	9	13	12	13	13	13	12	13	13	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
tonus	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Motoric, Exploration																																												
motoric	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	6	6	6	6	6	6	6	6	6	6	6	6	6	6
exploration behaviour	5	4	5	5	4	5	4	5	4	4	4	4	4	4	5	4	5	4	5	4	5	5	5	5	4	4	5	5	5	4	5	5	5	5	5	5	5	5	4	5
Exzitation																																												
exzitation	7	7	7	7	7	9	8	6	9	7	7	7	5	8	7	6	7	9	8	9	8	7	8	8	7	7	8	7	8	8	8	7	7	8	7	7	8	7	8	8
Abnormal Behaviour																																												
freezing, tremor	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
stereotypies, abnormal movement	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
sel- mutilation	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
urine and faeces	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	52	51	52	52	51	55	53	51	54	52	52	48	49	52	53	51	53	53	54	54	53	52	53	53	51	51	53	52	53	52	53	52	52	53	52	52	53	52	52	53

Table A7: Detailed clinical signs (IRWIN test), 4. week

DCS Irwin-Test

	Male																				Female																									
	E 791					E 792					E 793					E 794					E 795					E 796					E 797					E 798				
	High dose					Medium dose					Low dose					vehicle					High dose					Medium dose					Low dose					vehicle				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Appearence																																													
general status	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
physiologie/ autonomic functions	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
neurologie	12	12	12	12	13	13	12	12	13	12	12	12	12	12	13	13	12	11	13	12	13	12	13	12	12	12	13	12	12	13	12	12	12	13	12	12	12	12	12	12	12	12	12	12	12
tonus	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Motoric, Exploration																																													
motoric	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	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
exploration behaviour	5	5	5	5	5	4	4	4	5	5	4	4	5	5	5	5	4	4	5	5	4	4	4	4	4	5	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Exzitation																																													
exzitation	9	9	7	8	8	9	9	9	9	9	9	9	7	8	9	9	8	8	9	9	8	9	9	9	9	8	8	9	8	9	8	9	8	7	8	8	8	8	8	8					
Abnormal Behaviour																																													
freezing, tremor	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
stereotypies, abnormal movement	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
sel- mutilation	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
urine and faeces	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
	54	54	52	53	54	54	53	53	55	54	53	53	52	53	55	55	52	51	55	54	53	53	54	53	53	53	53	53	52	54	52	53	52	52	52	52	52	52	52	52					

Table A8: Organ weights, males

Group/Application	Animal	Body weight (at Necropsy)	Lymphnodes, axillary	rel. weight	Kidney (left)	rel. weight	Kidney (right)	rel. weight	Adrenal gland (left)	rel. weight	Adrenal gland (right)	rel. weight	Testis (left)	rel. weight	Testis (right)	rel. weight
Males																
High dose E 791	0	336	0,041	0,012	1,149	0,342	1,286	0,383	[illegible]	[illegible]	0,040	0,012	1,582	[illegible]	1,600	0,476
	1	312	0,030	0,010	1,287	0,413	1,369	0,439	0,027	0,009	0,026	0,008	1,862	0,597	1,798	0,576
	2	350	0,025	0,007	1,224	0,350	1,288	0,368	0,037	0,011	0,046	0,014	1,612	0,460	1,599	0,457
	3	304	0,033	0,011	1,199	0,394	1,253	0,412	0,029	0,010	0,028	0,009	1,570	0,516	1,610	0,530
	4	322	0,022	0,007	1,111	0,345	1,104	0,343	0,031	0,010	0,034	0,010	1,723	0,535	1,649	0,512
	Mean	325	0,030	0,009	1,194	0,369	1,260	0,389	0,032	0,010	0,035	0,011	1,670	0,516	1,651	0,510
	SD	18,5	0,006	0,002	0,068	0,032	0,097	0,037	0,004	0,001	0,009	0,002	0,123	0,055	0,084	0,047
	ttest geg	0,865	0,915	0,880	0,419	0,345	0,755	0,746	0,492	0,375	0,813	0,684	0,847	0,872	0,891	0,882
	Veh p=	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Medium dose E 792	0	363	0,046	0,013	1,324	0,365	1,314	0,362	0,030	0,008	0,036	0,010	1,597	0,440	1,525	0,420
	1	321	0,042	0,013	1,244	0,387	1,233	0,384	0,034	0,011	0,033	0,010	2,080	0,648	2,073	0,646
	2	321	0,051	0,016	1,173	0,365	1,218	0,379	0,033	0,010	0,029	0,009	2,109	0,657	2,136	0,665
	3	314	0,017	0,005	1,263	0,402	1,352	0,430	0,032	0,010	0,027	0,009	1,585	0,505	1,558	0,496
	4	311	0,047	0,015	1,105	0,355	1,081	0,347	0,024	0,008	0,028	0,009	1,511	0,486	1,585	0,510
	Mean	326	0,041	0,013	1,222	0,375	1,239	0,381	0,031	0,009	0,031	0,009	1,777	0,547	1,775	0,547
	SD	21,1	0,014	0,004	0,085	0,019	0,105	0,031	0,004	0,001	0,004	0,001	0,292	0,099	0,302	0,105
	ttest geg	0,813	0,231	0,253	0,697	0,419	0,966	0,878	0,299	0,263	0,317	0,138	0,508	0,564	0,329	0,433
	Veh p=	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Low dose E 793	0	342	0,051	0,015	1,315	0,385	1,360	0,398	0,039	0,011	0,032	0,009	1,809	0,529	1,812	0,530
	1	338	0,057	0,017	1,163	0,344	1,321	0,391	0,032	0,009	0,030	0,009	1,763	0,522	1,827	0,541
	2	322	0,019	0,006	1,302	0,404	1,219	0,379	0,032	0,010	0,025	0,008	1,687	0,524	1,665	0,517
	3	325	0,025	0,008	1,237	0,381	1,269	0,390	0,033	0,010	0,024	0,007	1,544	0,475	1,598	0,492
	4	320	0,025	0,008	1,252	0,391	1,262	0,394	0,023	0,007	0,031	0,010	1,832	0,573	1,860	0,581
	Mean	329	0,035	0,011	1,254	0,381	1,286	0,390	0,032	0,010	0,028	0,009	1,727	0,524	1,752	0,532
	SD	9,9	0,017	0,005	0,060	0,022	0,055	0,007	0,006	0,002	0,004	0,001	0,117	0,035	0,114	0,033
	ttest geg	0,598	0,629	0,706	0,947	0,669	0,463	0,277	0,524	0,379	0,046	0,032	0,553	0,810	0,117	0,293
	Veh p=	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	*	*	n.s.	n.s.	n.s.	n.s.
Vehicle E 794	0	326	0,028	0,008	1,246	0,382	1,298	0,398	0,029	0,009	0,033	0,010	1,705	0,523	1,709	0,524
	1	338	0,019	0,006	1,263	0,380	1,278	0,378	0,035	0,010	0,033	0,010	1,824	0,540	1,892	0,501
	2	309	0,025	0,008	1,079	0,349	1,155	0,374	0,044	0,014	0,030	0,010	1,636	0,529	1,705	0,552
	3	283	0,037	0,013	1,205	0,426	1,052	0,372	0,027	0,009	0,032	0,011	1,449	0,512	1,443	0,510
	4	355	0,047	0,013	1,434	0,404	1,400	0,394	0,038	0,011	0,033	0,009	1,765	0,497	1,575	0,444
	Mean	322	0,031	0,010	1,249	0,388	1,236	0,383	0,034	0,011	0,032	0,010	1,675	0,520	1,625	0,508
	SD	27,8	0,011	0,003	0,128	0,029	0,135	0,012	0,007	0,002	0,001	0,001	0,145	0,016	0,116	0,040

Group/Application	Animal	Prostata	rel. weight	Epididymis (left)	rel. weight	Epididymis (right)	rel. weight	Spleen	rel. weight	Liver	rel. weight	Thymus	rel. weight	Heart	rel. weight	Brain	rel. weight
Males																	
High dose E 791	0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	1	2,472	0,792	0,635	0,204	0,625	0,200	0,683	0,219	12,991	4,164	0,488	0,157	1,024	0,328	2,270	0,728
	2	2,405	0,687	0,597	0,171	0,609	0,174	0,754	0,215	14,336	4,096	0,358	0,102	1,179	0,337	2,074	0,593
	3	2,171	0,714	0,594	0,195	0,579	0,190	0,625	0,205	12,765	4,189	0,501	0,165	1,153	0,379	2,133	0,702
	4	2,016	0,626	0,585	0,182	0,608	0,189	0,628	0,195	11,802	3,665	0,600	0,186	1,040	0,323	2,133	0,662
	Mean	2,185	0,678	0,595	0,184	0,599	0,185	0,700	0,215	13,503	4,155	0,503	0,156	1,123	0,346	2,116	0,654
	SD	0,242	0,065	0,025	0,015	0,022	0,012	0,062	0,017	1,491	0,350	0,093	0,032	0,087	0,024	0,110	0,064
	ttest geg	0,369	0,346	0,338	0,330	0,970	0,852	0,402	0,317	0,763	0,700	0,271	0,372	0,945	0,933	0,548	0,861
	Veh p=	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Medium dose E 792	0	2,130	0,587	0,649	0,179	0,585	0,161	0,620	0,171	13,622	3,808	0,438	0,120	1,124	0,310	2,178	0,600
	1	2,108	0,657	0,610	0,190	0,585	0,182	0,568	0,177	11,497	3,582	0,278	0,087	1,003	0,312	2,096	0,653
	2	2,432	0,758	0,678	0,210	0,659	0,205	0,530	0,165	12,532	3,904	0,308	0,096	1,165	0,363	2,168	0,675
	3	1,724	0,549	0,536	0,171	0,520	0,165	0,668	0,213	12,706	4,047	0,356	0,113	1,110	0,354	2,328	0,741
	4	1,691	0,608	0,561	0,180	0,502	0,161	0,546	0,176	11,175	3,593	0,307	0,099	0,960	0,309	2,116	0,680
	Mean	2,057	0,632	0,606	0,188	0,570	0,175	0,586	0,180	12,346	3,787	0,337	0,103	1,072	0,329	2,177	0,670
	SD	0,288	0,080	0,058	0,015	0,062	0,019	0,057	0,019	1,053	0,201	0,062	0,013	0,087	0,027	0,091	0,051
	ttest geg	0,861	0,816	0,312	0,235	0,468	0,395	0,482	0,385	0,460	0,149	0,029	0,025	0,493	0,260	0,111	0,546
	Veh p=	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	*	*	n.s.	n.s.	n.s.	n.s.
Low dose E 793	0	1,928	0,564	0,605	0,177	0,651	0,190	0,692	0,202	13,467	3,938	0,399	0,117	1,163	0,348	2,238	0,654
	1	2,278	0,674	0,597	0,177	0,588	0,174	0,583	0,172	12,298	3,638	0,505	0,149	1,047	0,310	2,166	0,641
	2	2,295	0,713	0,689	0,214	0,645	0,200	0,682	0,212	12,793	3,973	0,455	0,141	1,113	0,346	2,022	0,628
	3	2,100	0,646	0,597	0,184	0,531	0,163	0,578	0,178	12,168	3,744	0,372	0,114	1,027	0,316	2,145	0,660
	4	2,148	0,671	0,592	0,185	0,573	0,179	0,772	0,241	13,551	4,235	0,471	0,147	1,075	0,336	2,019	0,631
	Mean	2,150	0,654	0,616	0,187	0,597	0,181	0,661	0,201	12,855	3,906	0,440	0,134	1,089	0,331	2,118	0,643
	SD	0,149	0,055	0,041	0,015	0,051	0,014	0,082	0,028	0,841	0,230	0,054	0,017	0,062	0,017	0,095	0,014
	ttest geg	0,449	0,535	0,163	0,191	0,947	0,650	0,737	0,826	0,759	0,401	0,944	0,740	0,826	0,217	0,490	0,651
	Veh p=	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Vehicle E 794	0	2,246	0,689	0,527	0,162	0,556	0,171	0,791	0,243	12,857	3,944	0,415	0,127	1,138	0,349	2,218	0,680
	1	2,025	0,599	0,573	0,170	0,599	0,177	0,735	0,217	13,655	4,039	0,398	0,118	1,258	0,372	1,986	0,588
	2	2,185	0,710	0,581	0,188	0,698	0,225	0,465	0,150	12,800	4,142	0,378	0,122	0,981	0,318	2,062	0,667
	3	1,463	0,517	0,489	0,173	0,539	0,190	0,518	0,183	10,217	3,610	0,511	0,180	1,027	0,363	2,034	0,719
	4	2,186	0,616	0,654	0,184	0,608	0,171	0,672	0,189	16,131	4,544	0,515	0,145	1,188	0,335	2,081	0,586
	Mean	2,023	0,628	0,565	0,175	0,600	0,187	0,636	0,197	13,172	4,068	0,443	0,138	1,118	0,347	2,078	0,646
	SD	0,324	0,077	0,062	0,011	0,061	0,023	0,140	0,035	2,133	0,338	0,065	0,028	0,114	0,022	0,067	0,059

n.s.: not significant. Asterisks denote statistical significance levels: *: p < 0,05, **: p < 0,01, ***: p < 0,001

[redacted]

Table A9: Organ weights, females

		Organ weight [g]																											
		Body weight (at Necropsy)	Lymphnodes, axillary	rel. weight	Kidney (left)	rel. weight	Kidney (right)	rel. weight	Adrenal gland (left)	rel. weight	Adrenal gland (right)	rel. weight	Spleen	rel. weight	Liver	rel. weight	Thymus	rel. weight	Heart	rel. weight	Brain	rel. weight	Ovar (left)	rel. weight	Ovar (right)	rel. weight	Uterus/ Cervix	rel. weight
Group/Application Females	Animal #																												
High dose E 795	0	222	0,028	0,013	0,855	0,402	0,879	0,396	0,049	0,022	0,050	0,023	0,523	0,236	9,774	4,403	0,440	0,198	1,002	0,451	1,917	0,864	0,058	0,026	0,077	0,035	0,450	0,203
	1	223	0,029	0,013	0,861	0,386	0,871	0,390	0,042	0,019	0,041	0,019	0,443	0,199	10,084	4,522	0,465	0,208	0,863	0,387	1,932	0,866	0,076	0,034	0,068	0,030	0,747	0,335
	2	225	0,032	0,014	0,858	0,381	0,985	0,438	0,043	0,019	0,042	0,018	0,410	0,182	8,859	3,937	0,354	0,158	0,939	0,418	1,889	0,840	0,069	0,031	0,035	0,016	0,476	0,211
	3	232	0,024	0,010	0,892	0,384	0,882	0,380	0,047	0,020	0,042	0,018	0,523	0,225	8,904	3,838	0,471	0,203	0,908	0,391	1,995	0,860	0,083	0,036	0,103	0,044	0,792	0,341
	4	233	0,016	0,007	0,817	0,351	0,792	0,340	0,047	0,020	0,041	0,017	0,426	0,183	10,419	4,472	0,445	0,191	0,736	0,316	2,030	0,871	0,067	0,029	0,076	0,033	0,347	0,149
	Mean	227	0,026	0,011	0,864	0,381	0,882	0,389	0,045	0,020	0,043	0,019	0,465	0,205	9,608	4,234	0,435	0,192	0,890	0,393	1,953	0,860	0,070	0,031	0,072	0,031	0,562	0,248
	SD	5,1	0,006	0,003	0,031	0,019	0,069	0,035	0,003	0,001	0,004	0,002	0,054	0,025	0,701	0,321	0,047	0,020	0,100	0,050	0,058	0,012	0,010	0,004	0,024	0,010	0,196	0,086
	ttest geg Veh p=	0,490 n.s.	0,021 *	0,031 *	0,372 n.s.	0,355 n.s.	0,943 n.s.	0,752 n.s.	0,795 n.s.	0,682 n.s.	0,812 n.s.	0,691 n.s.	0,364 n.s.	0,160 n.s.	0,099 n.s.	0,057 n.s.	0,930 n.s.	0,887 n.s.	0,565 n.s.	0,920 n.s.	0,282 n.s.	0,084 n.s.	0,121 n.s.	0,089 n.s.	0,409 n.s.	0,328 n.s.	0,234 n.s.	0,172 n.s.
Med dose E 796	0	225	0,028	0,012	0,771	0,343	0,807	0,359	0,047	0,021	0,045	0,020	0,588	0,261	7,332	3,259	0,324	0,144	0,969	0,431	1,956	0,869	0,090	0,040	0,101	0,045	0,761	0,338
	1	221	0,035	0,016	0,782	0,354	0,857	0,388	0,043	0,019	0,041	0,019	0,525	0,238	8,332	3,770	0,435	0,197	0,810	0,367	1,981	0,896	0,059	0,027	0,064	0,029	0,519	0,235
	2	209	0,030	0,014	0,853	0,408	0,953	0,456	0,052	0,025	0,055	0,026	0,523	0,250	7,741	3,704	0,455	0,218	0,763	0,365	2,027	0,970	0,062	0,030	0,062	0,030	1,110	0,531
	3	212	0,013	0,006	0,780	0,368	0,796	0,376	0,045	0,021	0,040	0,019	0,453	0,214	7,624	3,598	0,370	0,174	0,863	0,407	1,928	0,909	0,064	0,030	0,067	0,031	0,369	0,174
	4	225	0,027	0,012	0,865	0,384	0,892	0,396	0,059	0,026	0,062	0,027	0,466	0,207	8,838	3,928	0,466	0,207	0,957	0,425	2,029	0,902	0,083	0,037	0,086	0,038	1,081	0,481
	Mean	218	0,027	0,012	0,810	0,371	0,861	0,395	0,049	0,022	0,049	0,022	0,511	0,234	7,973	3,651	0,410	0,188	0,872	0,399	1,984	0,909	0,072	0,033	0,076	0,035	0,768	0,352
	SD	7,5	0,008	0,004	0,045	0,026	0,064	0,037	0,007	0,003	0,009	0,004	0,054	0,023	0,605	0,250	0,061	0,029	0,090	0,031	0,044	0,037	0,014	0,006	0,017	0,007	0,330	0,153
	ttest geg Veh p=	0,747 n.s.	0,037 *	0,034 *	0,825 n.s.	0,937 n.s.	0,797 n.s.	0,878 n.s.	0,654 n.s.	0,688 n.s.	0,598 n.s.	0,443 n.s.	0,751 n.s.	0,531 n.s.	0,483 n.s.	0,437 n.s.	0,656 n.s.	0,738 n.s.	0,778 n.s.	0,691 n.s.	0,490 n.s.	0,738 n.s.	0,189 n.s.	0,194 n.s.	0,513 n.s.	0,537 n.s.	0,820 n.s.	0,781 n.s.
Low dose E 797	0	226	0,032	0,014	0,867	0,383	0,899	0,398	0,049	0,022	0,037	0,016	0,459	0,203	8,492	3,758	0,408	0,181	0,957	0,424	2,032	0,899	0,076	0,034	0,094	0,041	0,534	0,236
	1	222	0,022	0,010	0,787	0,355	0,824	0,371	0,036	0,016	0,035	0,016	0,563	0,253	8,006	3,606	0,347	0,156	0,728	0,328	2,030	0,915	0,080	0,036	0,098	0,044	0,655	0,295
	2	228	0,034	0,015	0,907	0,398	0,976	0,428	0,045	0,020	0,034	0,015	0,452	0,198	9,775	4,287	0,417	0,183	1,017	0,446	1,992	0,874	0,102	0,045	0,088	0,038	0,458	0,201
	3	237	0,023	0,010	0,872	0,368	0,965	0,407	0,067	0,028	0,055	0,023	0,762	0,322	9,916	4,184	0,701	0,296	1,062	0,448	2,121	0,895	0,075	0,032	0,082	0,035	1,250	0,528
	4	201	0,032	0,016	0,814	0,405	0,808	0,402	0,039	0,019	0,039	0,019	0,432	0,215	8,100	4,030	0,353	0,176	0,822	0,409	1,967	0,978	0,058	0,029	0,049	0,024	0,424	0,211
	Mean	223	0,029	0,013	0,849	0,382	0,894	0,401	0,047	0,021	0,040	0,018	0,534	0,238	8,858	3,973	0,445	0,198	0,917	0,411	2,028	0,912	0,078	0,035	0,082	0,037	0,664	0,294
	SD	13,4	0,006	0,003	0,048	0,021	0,076	0,020	0,012	0,005	0,009	0,003	0,137	0,051	0,921	0,286	0,147	0,056	0,139	0,049	0,058	0,040	0,016	0,006	0,019	0,008	0,339	0,136
	ttest geg Veh p=	0,873 n.s.	0,005 **	0,008 **	0,574 n.s.	0,350 n.s.	0,795 n.s.	0,727 n.s.	0,988 n.s.	0,982 n.s.	0,530 n.s.	0,457 n.s.	0,621 n.s.	0,614 n.s.	0,547 n.s.	0,369 n.s.	0,856 n.s.	0,865 n.s.	0,411 n.s.	0,472 n.s.	0,948 n.s.	0,802 n.s.	0,482 n.s.	0,407 n.s.	0,925 n.s.	0,823 n.s.	0,735 n.s.	0,860 n.s.
Vehicle E 798	0	206	0,017	0,008	0,727	0,353	0,853	0,414	0,047	0,023	0,041	0,020	0,445	0,216	7,547	3,663	0,349	0,170	0,784	0,380	1,864	0,905	0,087	0,042	0,107	0,052	0,482	0,234
	1	246	0,017	0,007	0,958	0,390	1,053	0,428	0,066	0,027	0,056	0,023	0,589	0,239	9,640	3,919	0,563	0,229	0,808	0,329	2,139	0,869	0,075	0,030	0,084	0,034	1,009	0,410
	2	213	0,008	0,004	0,794	0,373	0,766	0,359	0,036	0,017	0,032	0,015	0,522	0,245	7,896	3,707	0,394	0,185	0,860	0,404	2,211	1,038	0,103	0,048	0,081	0,038	0,599	0,281
	3	209	0,019	0,009	0,746	0,357	0,778	0,372	0,028	0,013	0,033	0,016	0,465	0,223	7,191	3,441	0,387	0,185	0,909	0,435	1,920	0,919	0,062	0,030	0,060	0,029	0,853	0,408
	4	232	0,020	0,008	0,880	0,379	0,935	0,403	0,060	0,026	0,061	0,026	0,477	0,205	9,853	4,247	0,463	0,199	0,929	0,400	2,031	0,875	0,103	0,044	0,084	0,036	0,691	0,298
	Mean	221	0,016	0,007	0,821	0,370	0,877	0,395	0,047	0,021	0,045	0,020	0,499	0,226	8,425	3,795	0,431	0,194	0,858	0,390	2,033	0,921	0,086	0,039	0,083	0,038	0,727	0,326
	SD	17,2	0,005	0,002	0,097	0,015	0,120	0,029	0,016	0,006	0,013	0,005	0,057	0,016	1,234	0,304	0,084	0,022	0,062	0,039	0,145	0,066	0,018	0,008	0,017	0,009	0,206	0,079

n.s.: not significant. Asterisks denote significance levels: *: p < 0,05, **: p < 0,01, ***: p < 0,001

[redacted]

Table A10: Serum biochemistry, males

#	Dose	Sex	Animal ID	AP	AST	ALT	GGT	CHOL	KREA	HST	GLUC	ELALB	ALBGR	GLOBU	PROT	NA	K	CL	CA
code for the statistical analysis				4	4	4	2	4	2	4	4	4	4	4	4	4	4	4	4
21	HD	MM	11/791/0	126	80	32	<3	1,40	<0,2	6,52	9,10	39,6	2,2	18,00	58	127,8	3,96	83,8	2,60
22	HD	MM	11/791/1	130	80	30	<3	1,50	<0,2	7,36	9,44	41,8	2,6	16,08	58	135,4	3,72	90,8	2,76
23	HD	MM	11/791/2	110	114	34	<3	1,66	<0,2	8,00	11,32	41,4	2,2	18,82	60	141,2	6,54	90,2	2,68
24	HD	MM	11/791/3	176	68	30	<3	1,96	<0,2	6,40	9,88	39,8	2,5	15,92	56	140,2	4,26	91,0	2,72
25	HD	MM	11/791/4	118	78	44	<3	1,70	<0,2	6,72	10,44	36,0	2,3	15,65	52	124,6	4,14	84,8	2,48
			Mean	132,00	84,0	34,0	-	1,6	-	7,0	10,0	39,7	2,4	16,9	56,8	133,8	4,5	88,1	2,6
			StD	25,77	17,49	5,83	-	0,21	-	0,67	0,88	2,29	0,18	1,42	3,03	7,40	1,15	3,52	0,11
			Median	126,00	80,0	32,0	-	1,7	-	6,7	9,9	39,8	2,3	16,1	58,0	135,4	4,1	90,2	2,7
			Quantil 0,25	118,00	78,0	30,0	-	1,5	-	6,5	9,4	39,6	2,2	15,9	56,0	127,8	4,0	84,8	2,6
			Median - Mean	-5%	-5%	-6%	-	2%	-	-5%	-2%	0%	-4%	-5%	2%	1%	-11%	2%	2%
			p ttest vs vehicle	0,88	0,09	0,01	-	0,57	-	0,24	0,63	0,31	0,69	0,49	0,36	0,94	0,28	0,85	0,48
			Sig.	n.s.	n.s.	*	-	n.s.	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
26	MD	MM	11/792/0	146	62	16	<3	1,66	<0,2	7,02	11,32	40,4	2,1	19,24	60	137,4	3,98	91,2	2,70
27	MD	MM	11/792/1	108	78	18	<3	1,66	<0,2	6,20	10,00	46,6	2,4	19,42	66	138,2	4,14	88,6	2,68
28	MD	MM	11/792/2	92	70	18	<3	1,60	<0,2	5,26	9,10	38,6	2,2	17,55	56	126,8	4,24	79,0	2,42
29	MD	MM	11/792/3	156	76	14	<3	1,50	<0,2	6,92	10,10	43,2	3,4	12,71	56	139,0	4,08	93,8	2,64
30	MD	MM	11/792/4	122	60	16	<3	1,60	<0,2	6,22	8,88	39,6	2,2	18,00	58	138,4	4,60	88,0	2,76
			Mean	124,80	69,2	16,4	-	1,6	-	6,3	9,9	41,7	2,5	17,4	59,2	136,0	4,2	88,1	2,6
			StD	26,40	8,07	1,67	-	0,07	-	0,71	0,97	3,24	0,54	2,73	4,15	5,15	0,24	5,59	0,13
			Median	122,00	70,0	16,0	-	1,6	-	6,2	10,0	40,4	2,2	18,0	58,0	138,2	4,1	88,6	2,7
			Quantil 0,25	108,00	62,0	16,0	-	1,6	-	6,2	9,1	39,6	2,2	17,5	56,0	137,4	4,1	88,0	2,6
			Median - Mean	-2%	1%	-3%	-	-1%	-	-2%	1%	-3%	###	4%	-2%	2%	-2%	1%	2%
			p ttest vs vehicle	0,71	0,59	0,92	-	0,70	-	0,91	0,79	0,81	0,81	0,87	0,82	0,64	0,08	0,88	0,46
			Sig.	n.s.	n.s.	n.s.	-	n.s.	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
31	LD	MM	11/793/0	122	62	18	<3	1,60	<0,2	6,40	10,10	40,6	2,6	15,62	56	126,2	4,34	85,4	2,58
32	LD	MM	11/793/1	150	70	36	<3	1,50	<0,2	6,52	10,44	39,2	2,1	18,67	58	137,4	4,48	88,2	2,60
33	LD	MM	11/793/2	98	58	26	<3	1,40	<0,2	4,20	8,44	32,4	2,8	11,57	44	95,4	3,18	63,8	1,94
34	LD	MM	11/793/3	162	58	18	<3	1,56	<0,2	6,40	10,76	36,4	1,9	19,16	56	142,0	4,52	91,6	2,74
35	LD	MM	11/793/4	134	62	26	<3	1,56	<0,2	6,20	9,66	43,8	2,4	18,25	62	141,0	4,10	91,2	2,82
			Mean	133,20	62,0	24,8	-	1,5	-	5,9	9,9	38,5	2,4	16,7	55,2	128,4	4,1	84,0	2,5
			StD	24,88	4,90	7,43	-	0,08	-	0,98	0,90	4,32	0,36	3,15	6,72	19,48	0,55	11,59	0,35
			Median	134,00	62,0	26,0	-	1,6	-	6,4	10,1	39,2	2,4	18,3	56,0	137,4	4,3	88,2	2,6
			Quantil 0,25	122,00	58,0	18,0	-	1,5	-	6,2	9,7	36,4	2,1	15,6	56,0	126,2	4,1	85,4	2,6
			Median - Mean	1%	0%	5%	-	7%	-	9%	2%	2%	3%	10%	1%	7%	7%	5%	4%
			p ttest vs vehicle	0,81	0,55	0,20	-	0,64	-	0,47	0,79	0,22	0,82	0,56	0,29	0,54	0,48	0,53	0,33
			Sig.	n.s.	n.s.	n.s.	-	n.s.	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
36	VH	MM	11/794/0	112	50	24	<3	1,60	<0,2	5,90	8,88	37,8	2,3	16,43	54	127,0	3,78	84,0	2,56
37	VH	MM	11/794/1	142	60	22	<3	1,70	<0,2	6,60	10,32	49,2	2,4	20,50	70	134,6	3,90	88,8	2,88
38	VH	MM	11/794/2	118	82	2,8	<3	1,70	<0,2	7,26	11,22	43,4	2,6	16,69	60	143,4	4,00	92,0	2,84
39	VH	MM	11/794/3	136	68	26	<3	1,24	<0,2	5,16	10,10	37,6	2,3	16,35	54	129,6	3,74	82,0	2,50
40	VH	MM	11/794/4	142	68	10	<3	1,60	<0,2	7,00	7,88	43,6	2,4	18,17	62	136,4	4,22	91,4	2,80
			Mean	130,00	65,6	16,9	-	1,6	-	6,4	9,7	42,3	2,4	17,6	60,0	134,2	3,9	87,6	2,7
			StD	14,07	11,78	10,14	-	0,19	-	0,86	1,31	4,82	0,12	1,77	6,63	6,38	0,19	4,46	0,17
			Median	136,00	68,0	22,0	-	1,6	-	6,6	10,1	43,4	2,4	16,7	60,0	134,6	3,9	88,8	2,8
			Quantil 0,25	118,00	60,0	9,6	-	1,6	-	5,9	8,9	37,8	2,3	16,4	54,0	129,6	3,8	84,0	2,6
			Median - Mean	5%	4%	32%	-	6%	-	4%	5%	3%	0%	-6%	0%	0%	-1%	1%	5%
			Unit	U/l	U/l	U/l	U/l	mmol/l	µmol/l	mmol/l	mmol/l	g/l		g/l	g/l	mmol/l	mmol/l	mmol/l	mmol/l
legend for the statistical code				1 = no statistical analysis			2 = despriptive, no range				3= descriptive, range			4 = deductive, Bartletts, Anova, Dunnetts					

n.s.: not significant. Asterisks denote significance levels: *: p < 0,05, **: p < 0,01, ***: p < 0,001

[redacted]

Table A11: Serum biochemistry, females

#	Dose	Sex	Animal ID	AP	AST	ALT	GGT	CHOL	KREA	HST	GLUC	ELALB	ALBGR	GLOBU	PROT	NA	K	CL	CA
code for the statistical analysis				4	4	4	2	4	2	4	4	4	4	4	4	4	4	4	4
1	HD	FF	11/795/0	74	66	40	<3	1,86	<0,2	7,36	10,10	44,8	2,9	15,45	60	138,8	3,60	87,2	2,50
2	HD	FF	11/795/1	76	94	42	<3	1,56	<0,2	5,80	6,44	47,8	3,4	14,06	62	144,4	4,30	90,6	2,60
3	HD	FF	11/795/2	90	80	40	<3	1,34	<0,2	7,06	7,88	43,0	2,5	17,20	60	137,4	3,86	88,0	2,58
4	HD	FF	11/795/3	94	80	30	<3	1,50	<0,2	6,36	9,44	45,6	3,2	14,25	60	141,8	3,22	91,0	2,50
5	HD	FF	11/795/4	56	70	40	<3	1,56	<0,2	7,22	8,54	46,8	3,5	13,37	60	141,4	3,74	89,4	2,52
			Mean	78,00	78,0	38,4	-	1,6	-	6,8	8,5	45,6	3,1	14,9	60,4	140,8	3,7	89,2	2,5
			StD	15,03	10,86	4,77	-	0,19	-	0,66	1,42	1,85	0,41	1,50	0,89	2,73	0,39	1,63	0,05
			Median	76,00	80,0	40,0	-	1,6	-	7,1	8,5	45,6	3,2	14,3	60,0	141,4	3,7	89,4	2,5
			Quantil (0,25)	74,00	70,0	40,0	-	1,5	-	6,4	7,9	44,8	2,9	14,1	60,0	138,8	3,6	88,0	2,5
			Median - Mean	-3%	3%	4%	-	-1%	-	5%	1%	0%	5%	-4%	-1%	0%	0%	0%	-1%
			t-test vs vehicle (p)	0,21	0,04	0,83	-	0,37	-	0,42	0,26	0,50	0,60	0,42	0,26	0,60	0,59	0,14	0,41
			Sig.	n.s.	*	n.s.	-	n.s.	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
6	MD	FF	11/796/0	80	76	34	<3	1,40	<0,2	7,22	9,10	39,8	2,2	18,09	58	143,4	4,08	93,6	2,46
7	MD	FF	11/796/1	122	66	42	<3	1,18	<0,2	7,26	7,78	43,0	2,5	17,20	60	139,0	3,46	90,0	2,54
8	MD	FF	11/796/2	114	84	38	<3	1,40	<0,2	6,20	7,00	46,4	3,0	15,47	62	142,6	3,54	92,8	2,42
9	MD	FF	11/796/3	56	56	14	<3	1,24	<0,2	6,50	8,10	44,6	2,5	17,84	62	140,4	3,56	89,4	2,54
10	MD	FF	11/796/4	114	72	12	<3	2,12	<0,2	5,70	9,10	46,6	3,0	15,53	62	140,4	4,50	90,0	2,56
			Mean	97,20	70,8	28,0	-	1,5	-	6,6	8,2	44,1	2,6	16,8	60,8	141,2	3,8	91,2	2,5
			StD	28,16	10,55	14,00	-	0,38	-	0,67	0,90	2,81	0,35	1,25	1,79	1,80	0,45	1,90	0,06
			Median	114,00	72,0	34,0	-	1,4	-	6,5	8,1	44,6	2,5	17,2	62,0	140,4	3,6	90,0	2,5
			Quantil 0,25	80,00	66,0	14,0	-	1,2	-	6,2	7,8	43,0	2,5	15,5	60,0	140,4	3,5	90,0	2,5
			Median - Mean	17%	2%	22%	-	-15%	-	-1%	-2%	1%	-9%	2%	2%	-1%	-9%	-1%	2%
			p ttest vs vehicle	0,05	0,21	0,20	-	0,80	-	0,67	0,08	0,17	0,13	0,29	0,40	0,73	0,42	0,67	0,14
			Sig.	n.s.	n.s.	n.s.	-	n.s.	-	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
11	LD	FF	11/797/0	110	80	14	<3	1,76	<0,2	5,82	6,32	42,4	2,2	19,27	62	141,4	3,82	90,2	2,48
12	LD	FF	11/797/1	108	76	30	<3	1,56	<0,2	6,16	7,78	41,4	2,2	18,82	60	142,8	3,68	93,0	2,54
13	LD	FF	11/797/2	64	74	38	<3	1,24	<0,2	8,70	10,10	45,6	2,5	18,24	64	139,2	3,86	89,4	2,52
14	LD	FF	11/797/3	56	52	40	<3	1,40	<0,2	5,82	8,44	45,8	2,5	18,32	64	146,0	3,62	93,2	2,66
15	LD	FF	11/797/4	112	74	28	<3	1,50	<0,2	7,12	7,10	45,8	2,8	16,36	62	141,6	4,30	90,4	2,56
			Mean	90,00	71,2	30,0	-	1,5	-	6,7	7,9	44,2	2,4	18,2	62,4	142,2	3,9	91,2	2,6
			StD	27,57	11,01	10,30	-	0,19	-	1,23	1,44	2,13	0,25	1,11	1,67	2,49	0,27	1,74	0,07
			Median	108,00	74,0	30,0	-	1,5	-	6,2	7,8	45,6	2,5	18,3	62,0	141,6	3,8	90,4	2,5
			Quantil 0,25	64,00	74,0	28,0	-	1,4	-	5,8	7,1	42,4	2,2	18,2	62,0	141,4	3,7	90,2	2,5
			Median - Mean	20%	4%	0%	-	2%	-	-10%	-2%	3%	4%	1%	-1%	0%	-1%	-1%	-1%
			p ttest vs vehicle	0,12	0,20	0,20	-	0,63	-	0,60	0,09	0,13	0,01	0,03	1,00	0,69	0,24	0,59	0,65
			Sig.	n.s.	n.s.	n.s.	-	n.s.	-	n.s.	n.s.	n.s.	*	*	n.s.	n.s.	n.s.	n.s.	n.s.
16	VH	FF	11/798/0	50	54	42	<3	1,08	<0,2	6,02	9,00	44,6	3,3	13,52	58	138,8	3,36	89,6	2,52
17	VH	FF	11/798/1	76	70	46	<3	1,56	<0,2	5,16	8,00	44,6	2,6	17,15	62	142,4	4,16	90,0	2,62
18	VH	FF	11/798/2	62	52	30	<3	1,82	<0,2	6,82	9,54	48,4	2,8	17,29	66	142,6	3,52	90,2	2,60
19	VH	FF	11/798/3	60	74	38	<3	1,46	<0,2	7,00	10,22	45,6	3,2	14,25	60	140,2	3,68	91,4	2,48
20	VH	FF	11/798/4	82	60	32	<3	1,14	<0,2	6,86	10,32	49,4	3,0	16,47	66	144,0	3,36	92,4	2,64
			Mean	66,00	62,0	37,6	-	1,4	-	6,4	9,4	46,5	3,0	15,7	62,4	141,6	3,6	90,7	2,6
			StD	12,88	9,70	6,69	-	0,31	-	0,78	0,96	2,24	0,29	1,74	3,58	2,07	0,33	1,15	0,07
			Median	62,00	60,0	38,0	-	1,5	-	6,8	9,5	45,6	3,0	16,5	62,0	142,4	3,5	90,2	2,6
			Quantil 0,25	60,00	54,0	32,0	-	1,1	-	6,0	9,0	44,6	2,8	14,3	60,0	140,2	3,4	90,0	2,5
			Median - Mean	-6%	-3%	1%	-	12%	-	8%	1%	-2%	1%	5%	-1%	1%	-4%	-1%	2%
			Unit	U/l	U/l	U/l	U/l	mmol/l	µmol/l	mmol/l	mmol/l	g/l		g/l	g/l	mmol/l	mmol/l	mmol/l	mmol/l
legend for the statistical code				1 = no statistical analysis			2 = despriptive, no range				3= descriptive, range			4 = deductive, Bartletts, Anova, Dunnetts					

n.s.: not significant. Asterisks denote significance levels: *: $p < 0,05$, **: $p < 0,01$, ***: $p < 0,001$

[redacted]

Table A12: Haematology and blood clotting time, males

#	Dose	Sex	Animal ID	LEU	ERY	HB	HKT	MCV	MCH	MCHC	THR	RETIR	RETIRA	NEU	NEU2	LYM	MON	EOS	BAS	OTH	NEUA	NEU2A	LYMA	MONA	EOSA	BASA	OTHA	TPZ1
code for the statistical analysis				4	4	4	4	4	4	4	4	4	4	4	2	4	3	3	3	3	1	1	1	1	1	1	1	3
21	HD	MM	11/791/0	11	8,6	158	0,49	57	18	32,4	768	31	267220	12	0	85	2	1	0	1	1344	0	9520	224	112	0	112	77
22	HD	MM	11/791/1	8	8,7	157	0,47	54	18	33	852	29	252590	18	0	79	1	1	0	0	1512	0	6636	84	84	0	0	62
23	HD	MM	11/791/2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24	HD	MM	11/791/3	8	8,9	157	0,48	54	18	33	959	35	310450	15	0	82	2	1	0	1	1245	0	6806	166	83	0	83	69
25	HD	MM	11/791/4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Mean	9,3	8,7	157,3	0,48	54,9	18,0	33	859,7	31,7	276753,3	15,0	0,0	82,0	1,7	1,0	0,0	0,7	-	-	-	-	-	-	-	69,2
			StD	1,65	0,13	0,58	0,01	1,42	0,30	1	95,73	3,06	30085,02	3,00	0,00	3,00	0,58	0,00	0,00	0,58	-	-	-	-	-	-	-	7,87
			Median	8,4	8,7	157,0	0,48	54,1	18,0	33	852,0	31,0	267220,0	15,0	0,0	82,0	2,0	1,0	0,0	1,0	-	-	-	-	-	-	-	68,5
			Quantil 0,25	8,4	8,7	157,0	0,48	54,1	17,9	33	810,0	30,0	259905,0	13,5	0,0	80,5	1,5	1,0	0,0	0,5	-	-	-	-	-	-	-	65,1
			Median - Mean	-11%	0%	0%	0,00	-1%	0%	0%	-1%	-2%	-3%	0%	0%	0%	50%	-	0%	-100%	-	-	-	-	-	-	-	-1%
			p ttest vs vehicle	0,42	0,24	0,62	0,85	0,14	0,14	0,83	0,72	0,07	0,07	0,87	-	0,70	-	-	-	-	-	-	-	-	-	-	-	-
			Sig.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	-	-	-	-	-	-	-	-	-	-	-	-
26	MD	MM	11/792/0	8	9,3	154	0,47	51	17	32,7	1003	32	296640	10	0	86	1	2	0	1	840	0	7224	84	168	0	84	66
27	MD	MM	11/792/1	9	9,4	160	0,48	52	17	33	907	29	272310	8	0	89	1	1	0	1	736	0	8188	92	92	0	92	77
28	MD	MM	11/792/2	9	9,2	161	0,51	55	17	32	832	31	286130	13	0	83	1	1	0	1	1131	0	7221	87	87	0	87	61
29	MD	MM	11/792/3	9	8,7	148	0,46	53	17	33	833	27	233820	9	0	87	1	2	0	0	837	0	8091	93	186	0	0	64
30	MD	MM	11/792/4	9	9,0	156	0,47	52	17	33	961	25	226000	8	0	88	2	2	0	1	744	0	8184	186	186	0	93	69
			Mean	9,0	9,1	155,8	0,48	52,4	17,1	33	907,2	28,8	262980,0	9,6	0,0	86,6	1,2	1,6	0,0	0,8	-	-	-	-	-	-	-	67,4
			StD	0,41	0,29	5,22	0,02	1,52	0,31	1	76,21	2,86	31519,01	2,07	0,00	2,30	0,45	0,55	0,00	0,45	-	-	-	-	-	-	-	6,04
			Median	9,2	9,2	156,0	0,47	52,2	17,1	33	907,0	29,0	272310,0	9,0	0,0	87,0	1,0	2,0	0,0	1,0	-	-	-	-	-	-	-	66,0
			Quantil 0,25	8,7	9,0	154,0	0,47	51,5	17,0	33	833,0	27,0	233820,0	8,0	0,0	86,0	1,0	1,0	0,0	1,0	-	-	-	-	-	-	-	64,4
			Median - Mean	3%	1%	0%	0,02	0%	0%	0%	0%	1%	4%	-7%	0%	0%	-100%	67%	0%	-100%	-	-	-	-	-	-	-	-2%
			p ttest vs vehicle	0,36	0,21	0,95	1,00	0,18	0,10	0,78	0,62	0,28	0,17	0,23	-	0,22	-	-	-	-	-	-	-	-	-	-	-	-
			Sig.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	-	-	-	-	-	-	-	-	-	-	-	-
31	LD	MM	11/793/0	10	8,4	150	0,44	53	18	33,9	781	29	242150	11	0	86	1	2	0	1	1056	0	8256	96	192	0	96	49
32	LD	MM	11/793/1	7	8,9	162	0,49	55	18	33	942	28	248920	11	0	86	1	2	0	1	781	0	6106	71	142	0	71	56
33	LD	MM	11/793/2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
34	LD	MM	11/793/3	8	9,0	158	0,48	53	18	33	958	27	243270	13	0	85	1	1	0	0	1027	0	6715	79	79	0	0	78
35	LD	MM	11/793/4	9	9,1	156	0,48	53	17	33	905	31	280550	16	0	81	2	1	0	0	1408	0	7128	176	88	0	0	62
			Mean	8,4	8,8	156,5	0,47	53,4	17,7	33	896,5	28,8	253722,5	12,8	0,0	84,5	1,3	1,5	0,0	0,5	-	-	-	-	-	-	-	61,2
			StD	1,08	0,32	5,00	0,02	0,77	0,46	1	80,14	1,71	18128,76	2,36	0,00	2,38	0,50	0,58	0,00	0,58	-	-	-	-	-	-	-	12,57
			Median	8,4	9,0	157,0	0,48	53,1	17,8	33	923,5	28,5	246095,0	12,0	0,0	85,5	1,0	1,5	0,0	0,5	-	-	-	-	-	-	-	58,8
			Quantil 0,25	7,7	8,8	154,5	0,47	53,0	17,4	33	874,0	27,8	242990,0	11,0	0,0	84,0	1,0	1,0	0,0	0,0	-	-	-	-	-	-	-	54,1
			Median - Mean	0%	2%	0%	-0,01	-1%	0%	0%	3%	-1%	-3%	-6%	0%	1%	-100%	0%	0%	0%	-	-	-	-	-	-	-	-4%
			p ttest vs vehicle	0,69	0,66	0,88	0,67	0,80	0,51	0,24	0,79	0,26	0,26	0,57	-	0,42	-	-	-	-	-	-	-	-	-	-	-	-
			Sig.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	-	-	-	-	-	-	-	-	-	-	-	-
36	VH	MM	11/794/0	8	8,9	150	0,47	53	17	32,1	855	25	222750	11	0	84	1	3	0	1	891	0	6804	81	243	0	81	135
37	VH	MM	11/794/1	10	8,8	156	0,48	54	18	33	806	26	229320	14	0	82	2	1	0	1	1330	0	7790	190	95	0	95	71
38	VH	MM	11/794/2	3	9,1	161	0,50	55	18	32	999	24	219360	36	0	56	3	4	0	0	972	0	1512	81	108	0	0	78
39	VH	MM	11/794/3	9	9,0	159	0,48	53	18	33	841	26	234780	9	0	88	1	2	0	0	801	0	7832	89	178	0	0	78
40	VH	MM	11/794/4	9	8,6	154	0,46	54	18	33	911	32	275840	11	0	84	3	1	0	1	1034	0	7896	282	94	0	94	63
			Mean	7,7	8,9	156,0	0,48	53,5	17,5	33	882,4	26,6	236410,0	16,2	0,0	78,8	2,0	2,2	0,0	0,6	-	-	-	-	-	-	-	84,8
			StD	2,86	0,20	4,30	0,01	0,86	0,42	1	75,36	3,13	22830,62	11,21	0,00	12,93	1,00	1,30	0,00	0,55	-	-	-	-	-	-	-	28,75
			Median	8,9	8,9	156,0	0,48	53,6	17,6	33	855,0	26,0	229320,0	11,0	0,0	84,0	2,0	2,0	0,0	1,0	-	-	-	-	-	-	-	77,6
			Quantil 0,25	8,1	8,8	154,0	0,47	52,9	17,6	32	841,0	25,0	222750,0	11,0	0,0	82,0	1,0	1,0	0,0	0,0	-	-	-	-	-	-	-	70,8
			Median - Mean	18%	0%	0%	0,00	0%	0%	0%	-3%	-2%	-3%	-34%	0%	7%	0%	-17%	0%	-100%	-	-	-	-	-	-	-	-9%
			Unit	G/l	T/l	g/l	l/l	fl	pg	g/dl	G/l	promille	/µl	%	%	%	%	%	%	%	/µl	/µl	/µl	/µl	/µl	/µl	/µl	s

legend for the statistical code: 1 = no statistical analysis; 2 = despriptive, no range; 3= descriptive, range; 4 = deductive, Bartletts, Anova, Dunnetts

n.s.: not significant. Asterisks denote significance levels: *: p < 0,05, **: p < 0,01, ***: p < 0,001

[redacted]

Table A13: Haematology and blood clotting time, females

#	Dose	Sex	Animal ID	LEU	ERY	HB	HKT	MCV	MCH	MCHC	THR	RETIR	RETIRA	NEU	NEU2	LYM	MON	EOS	BAS	OTH	NEUA	NEU2A	LYMA	MONA	EOSA	BASA	OTHA	TPZ1
code for the statistical analysis				4	4	4	4	4	4	4	4	4	4	4	2	4	3	3	3	3	1	1	1	1	1	1	1	3
1	HD	FF	11/795/0	8	8,3	147	0,44	53	18	33,6	831	31	258540	11	0	85	2	2	0	1	825	0	6375	150	150	0	75	160
2	HD	FF	11/795/1	3	8,6	153	0,48	56	18	32	731	35	301000	12	0	81	3	3	0	1	384	0	2592	96	96	0	32	53
3	HD	FF	11/795/2	6	9,2	156	0,48	52	17	33	939	27	248130	20	0	76	2	2	0	0	1280	0	4864	128	128	0	0	54
4	HD	FF	11/795/3	3	8,2	146	0,46	56	18	32	868	36	296280	12	0	85	2	2	0	0	396	0	2805	66	66	0	0	53
5	HD	FF	11/795/4	4	8,3	151	0,46	56	18	33	971	30	248100	9	0	89	1	1	0	1	369	0	3649	41	41	0	41	59
			Mean	4,9	8,5	150,6	0,46	54,2	17,7	33	868,0	31,8	270410,0	12,8	0,0	83,2	2,0	2,0	0,0	0,6	-	-	-	-	-	-	-	75,9
			StD	1,94	0,40	4,16	0,02	1,87	0,47	1	94,59	3,70	26172,68	4,21	0,00	4,92	0,71	0,71	0,00	0,55	-	-	-	-	-	-	-	47,10
			Median	4,1	8,3	151,0	0,46	55,5	17,7	33	868,0	31,0	258540,0	12,0	0,0	85,0	2,0	2,0	0,0	1,0	-	-	-	-	-	-	-	53,8
			Quantil (0,25)	3,3	8,3	147,0	0,46	52,5	17,6	32	831,0	30,0	248130,0	11,0	0,0	81,0	2,0	2,0	0,0	0,0	-	-	-	-	-	-	-	53,4
			Median - Mean	-21%	-2%	0%	0,01	2%	0%	0%	0%	-3%	-4%	-7%	0%	2%	0%	0%	0%	-100%	-	-	-	-	-	-	-	-29%
			t-test vs vehicle (p)	0,15	0,64	0,88	0,58	0,78	0,44	0,54	0,98	0,24	0,22	0,43	-	0,61	-	-	-	-	-	-	-	-	-	-	-	-
			Sig.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	-	-	-	-	-	-	-	-	-	-	-	-
6	MD	FF	11/796/0	4	8,0	148	0,45	57	19	32,8	828	29	231130	11	0	85	1	2	0	1	429	0	3315	39	78	0	39	64
7	MD	FF	11/796/1	8	8,6	157	0,47	55	18	33	763	26	222820	10	0	87	1	1	0	1	760	0	6612	76	76	0	76	135
8	MD	FF	11/796/2	3	8,3	153	0,46	56	19	33	822	30	248400	15	0	81	2	2	0	1	465	0	2511	62	62	0	31	63
9	MD	FF	11/796/3	4	8,8	154	0,46	53	18	33	961	26	228020	10	0	86	1	2	0	0	380	0	3268	38	76	0	0	76
10	MD	FF	11/796/4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Mean	4,6	8,4	153,0	0,46	55,1	18,3	33	843,5	27,8	232592,5	11,5	0,0	84,8	1,3	1,8	0,0	0,8	-	-	-	-	-	-	-	84,2
			StD	2,03	0,35	3,74	0,01	1,76	0,45	0	83,64	2,06	11081,90	2,38	0,00	2,63	0,50	0,50	0,00	0,50	-	-	-	-	-	-	-	34,10
			Median	3,9	8,4	153,5	0,46	55,5	18,4	33	825,0	27,5	229575,0	10,5	0,0	85,5	1,0	2,0	0,0	1,0	-	-	-	-	-	-	-	69,7
			Quantil 0,25	3,6	8,2	151,8	0,46	54,5	18,1	33	807,3	26,0	226720,0	10,0	0,0	84,0	1,0	1,8	0,0	0,8	-	-	-	-	-	-	-	63,6
			Median - Mean	-21%	0%	0%	0,00	1%	1%	0%	-2%	-1%	-1%	-10%	0%	1%	-100%	33%	0%	-100%	-	-	-	-	-	-	-	-17%
			p ttest vs vehicle	0,12	0,97	0,38	0,83	0,85	0,58	0,81	0,60	0,26	0,34	0,78	-	0,94	-	-	-	-	-	-	-	-	-	-	-	-
			Sig.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	-	-	-	-	-	-	-	-	-	-	-	-
11	LD	FF	11/797/0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12	LD	FF	11/797/1	6	8,3	156	0,47	57	19	33	937	28	232120	7	0	90	1	1	0	1	406	0	5220	58	58	0	58	66
13	LD	FF	11/797/2	7	8,1	146	0,43	53	18	34	943	31	250790	8	0	90	1	1	0	1	560	0	6300	70	70	0	70	60
14	LD	FF	11/797/3	6	7,9	144	0,43	54	18	34	819	31	245210	10	0	87	1	2	0	1	550	0	4785	55	110	0	55	48
15	LD	FF	11/797/4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Mean	6,1	8,1	148,7	0,44	54,8	18,3	34	899,7	30,0	242706,7	8,3	0,0	89,0	1,0	1,3	0,0	1,0	-	-	-	-	-	-	-	58,1
			StD	0,79	0,19	6,43	0,02	2,10	0,42	1	69,92	1,73	9583,44	1,53	0,00	1,73	0,00	0,58	0,00	0,00	-	-	-	-	-	-	-	9,33
			Median	5,8	8,1	146,0	0,43	54,1	18,2	34	937,0	31,0	245210,0	8,0	0,0	90,0	1,0	1,0	0,0	1,0	-	-	-	-	-	-	-	60,2
			Quantil 0,25	5,7	8,0	145,0	0,43	53,7	18,1	33	878,0	29,5	238665,0	7,5	0,0	88,5	1,0	1,0	0,0	1,0	-	-	-	-	-	-	-	54,1
			Median - Mean	-6%	0%	-2%	0,02	-1%	-1%	1%	4%	3%	1%	-5%	0%	1%	-	-100%	0%	-	-	-	-	-	-	-	-	4%
			p ttest vs vehicle	0,58	0,25	0,49	0,33	0,81	0,51	0,46	0,42	0,68	0,78	0,13	-	0,08	-	-	-	-	-	-	-	-	-	-	-	-
			Sig.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-	n.s.	-	-	-	-	-	-	-	-	-	-	-	-
16	VH	FF	11/798/0	5	8,6	148	0,47	54	17	31,8	807	30	258300	15	0	79	1	4	0	0	795	0	4187	53	212	0	0	160
17	VH	FF	11/798/1	7	7,9	151	0,45	57	19	33	866	27	213840	9	0	88	1	1	0	1	657	0	6424	73	73	0	73	60
18	VH	FF	11/798/2	9	8,8	155	0,48	55	18	32	895	32	282560	10	0	85	2	2	0	1	860	0	7310	172	172	0	86	109
19	VH	FF	11/798/3	5	8,1	149	0,44	54	18	34	853	28	226520	11	0	85	2	2	0	1	583	0	4505	106	106	0	53	63
20	VH	FF	11/798/4	7	8,6	152	0,45	52	18	34	912	30	257400	10	0	86	1	2	0	1	660	0	5676	66	132	0	66	124
			Mean	6,6	8,4	151,0	0,46	54,5	18,0	33	866,6	29,4	247724,0	11,0	0,0	84,6	1,4	2,2	0,0	0,8	-	-	-	-	-	-	-	103,3
			StD	1,40	0,38	2,74	0,02	1,69	0,75	1	40,64	1,95	27462,51	2,35	0,00	3,36	0,55	1,10	0,00	0,45	-	-	-	-	-	-	-	42,11
			Median	6,6	8,6	151,0	0,45	54,4	17,7	33	866,0	30,0	257400,0	10,0	0,0	85,0	1,0	2,0	0,0	1,0	-	-	-	-	-	-	-	109,1
			Quantil 0,25	5,3	8,1	149,0	0,45	54,0	17,6	32	853,0	28,0	226520,0	10,0	0,0	85,0	1,0	2,0	0,0	1,0	-	-	-	-	-	-	-	63,4
			Median - Mean	0%	2%	0%	0,01	0%	-2%	1%	0%	2%	4%	-10%	0%	0%	-100%	-17%	0%	-100%	-	-	-	-	-	-	-	6%
			Unit	G/l	T/l	g/l	Vl	fl	pg	g/dl	G/l	promille	/µl	%	%	%	%	%	%	%	/µl	/µl	/µl	/µl	/µl	/µl	/µl	s

legend for the statistical code: 1 = no statistical analysis; 2 = despriptive, no range; 3= descriptive, range; 4 = deductive, Bartletts, Anova, Dunnetts

n.s.: not significant. Asterisks denote significance levels: *: p < 0,05, **: p < 0,01, ***: p < 0,001

[redacted]

Table A14: Statistics, blood analysis, males

Analysed parameter	One-way analysis of variance P	Sig.	F	R sq.	Bartlett's test for equal variances B.'s statistic (corr.)	P	Sig.	Dunnett's Multiple Comparison Test	Mean Diff	q	Sig.	95% CI of diff
M AP	0,9431	ns	0,1263	0,02314	1,587	0,6623	ns	VH vs LD	-3,2	0,2168	ns	-41,46 to 35,06
								VH vs MD	5,2	0,3523	ns	-33,06 to 43,46
								VH vs HD	-2	0,1355	ns	-40,26 to 36,26
M AST	0,0403	*	3,494	0,3958	5,667	0,129	ns	VH vs LD	3,6	0,4926	ns	-15,34 to 22,54
								VH vs MD	-3,6	0,4926	ns	-22,54 to 15,34
								VH vs HD	-18,4	2,518	ns	-37,34 to 0,5440
M ALT	0,0031	**	7,076	0,5702	8,378	0,0388	*	VH vs LD	-7,8	1,78	ns	-19,16 to 3,559
								VH vs MD	0,6	0,1369	ns	-10,76 to 11,96
								VH vs HD	-17	3,88	**	-28,36 to -5,641
M CHOL	0,6448	ns	0,5668	0,09606	6,831	0,0775	ns	VH vs LD	0,044	0,4578	ns	-0,2051 to 0,2931
								VH vs MD	-0,036	0,3746	ns	-0,2851 to 0,2131
								VH vs HD	-0,076	0,7908	ns	-0,3251 to 0,1731
M HST	0,2668	ns	1,445	0,2132	0,6797	0,878	ns	VH vs LD	0,44	0,8557	ns	-0,8931 to 1,773
								VH vs MD	0,06	0,1167	ns	-1,273 to 1,393
								VH vs HD	-0,616	1,198	ns	-1,949 to 0,7171
M GLUC	0,9584	ns	0,1007	0,01853	0,8011	0,8492	ns	VH vs LD	-0,2	0,3076	ns	-1,885 to 1,485
								VH vs MD	-0,2	0,3076	ns	-1,885 to 1,485
								VH vs HD	-0,356	0,5476	ns	-2,041 to 1,329
M ELALB	0,3834	ns	1,086	0,1692	2,136	0,5447	ns	VH vs LD	3,84	1,6	ns	-2,382 to 10,06
								VH vs MD	0,64	0,2666	ns	-5,582 to 6,862
								VH vs HD	2,6	1,083	ns	-3,622 to 8,822
M ALBGR	0,9616	ns	0,09524	0,01754	8,33	0,0397	*	VH vs LD	0,04	0,1847	ns	-0,5214 to 0,6014
								VH vs MD	-0,06	0,2771	ns	-0,6214 to 0,5014
								VH vs HD	0,04	0,1847	ns	-0,5214 to 0,6014
M GLOBU	0,9113	ns	0,1757	0,03189	2,784	0,4261	ns	VH vs LD	0,974	0,6485	ns	-2,920 to 4,868
								VH vs MD	0,244	0,1625	ns	-3,650 to 4,138
								VH vs HD	0,734	0,4887	ns	-3,160 to 4,628
M PROT	0,4918	ns	0,8397	0,136	2,884	0,4099	ns	VH vs LD	4,8	1,412	ns	-4,014 to 13,61
								VH vs MD	0,8	0,2353	ns	-8,014 to 9,614
								VH vs HD	3,2	0,9412	ns	-5,614 to 12,01
M NA	0,7373	ns	0,4257	0,07392	8,695	0,0336	*	VH vs LD	5,8	0,819	ns	-12,56 to 24,16
								VH vs MD	-1,76	0,2485	ns	-20,12 to 16,60
								VH vs HD	0,36	0,0508	ns	-18,00 to 18,72
M K	0,5546	ns	0,7198	0,1189	13,32	0,004	**	VH vs LD	-0,196	0,4738	ns	-1,268 to 0,8763
								VH vs MD	-0,28	0,6769	ns	-1,352 to 0,7923
								VH vs HD	-0,596	1,441	ns	-1,668 to 0,4763
M CL	0,7594	ns	0,3935	0,06871	6,361	0,0953	ns	VH vs LD	3,6	0,8093	ns	-7,931 to 15,13
								VH vs MD	-0,48	0,1079	ns	-12,01 to 11,05
								VH vs HD	-0,48	0,1079	ns	-12,01 to 11,05
M CA	0,6169	ns	0,6122	0,103	6,121	0,1058	ns	VH vs LD	0,18	1,341	ns	-0,1681 to 0,5281
								VH vs MD	0,076	0,566	ns	-0,2721 to 0,4241
								VH vs HD	0,068	0,5064	ns	-0,2801 to 0,4161
M LEU	0,606	ns	0,6343	0,1277	1)			VH vs LD	-0,63	0,5204	ns	-3,844 to 2,584
								VH vs MD	-1,26	1,104	ns	-4,290 to 1,770
								VH vs HD	-1,58	1,199	ns	-5,079 to 1,919
M ERY	0,2041	ns	1,761	0,2889	1)			VH vs LD	0,079	0,4656	ns	-0,3714 to 0,5294
								VH vs MD	-0,214	1,338	ns	-0,6386 to 0,2106
								VH vs HD	0,1707	0,924	ns	-0,3196 to 0,6610
M HB	0,9671	ns	0,08488	0,01921	1)			VH vs LD	-0,5	0,1672	ns	-8,440 to 7,440
								VH vs MD	0,2	0,0709	ns	-7,286 to 7,686
								VH vs HD	-1,333	0,4095	ns	-9,977 to 7,311
M HKT	0,9426	ns	0,1267	0,0284	1)			VH vs LD	0,0055	0,4654	ns	-0,02587 to 0,03687
								VH vs MD	0	0	ns	-0,02958 to 0,02958
								VH vs HD	-0,002	0,1554	ns	-0,03615 to 0,03215
M MCV	0,0796	ns	2,831	0,3952	1)			VH vs LD	0,145	0,184	ns	-1,947 to 2,237
								VH vs MD	1,14	1,534	ns	-0,8328 to 3,113
								VH vs HD	-1,347	1,569	ns	-3,625 to 0,9313
M MCH	0,0286	*	4,159	0,4898	1)			VH vs LD	-0,205	0,7986	ns	-0,8864 to 0,4764
								VH vs MD	0,44	1,818	ns	-0,2024 to 1,082
								VH vs HD	-0,48	1,718	ns	-1,222 to 0,2618
M MCHC	0,455	ns	0,9276	0,1763	1)			VH vs LD	-0,485	1,314	ns	-1,465 to 0,4951
								VH vs MD	0,1	0,2873	ns	-0,8240 to 1,024
								VH vs HD	-0,09334	0,2322	ns	-1,160 to 0,9736
M THR	0,865	ns	0,2428	0,05305	1)			VH vs LD	-14,1	0,2622	ns	-156,8 to 128,6
								VH vs MD	-24,8	0,4891	ns	-159,4 to 109,8
								VH vs HD	22,73	0,3883	ns	-132,7 to 178,1
M RETIR	0,148	ns	2,113	0,3277	1)			VH vs LD	-2,15	1,159	ns	-7,074 to 2,774
								VH vs MD	-2,2	1,258	ns	-6,843 to 2,443
								VH vs HD	-5,067	2,509	ns	-10,43 to 0,2943
M NEU	0,4496	ns	0,9398	0,1782	1)			VH vs LD	3,45	0,7873	ns	-8,182 to 15,08
								VH vs MD	6,6	1,597	ns	-4,367 to 17,57
								VH vs HD	1,2	0,2515	ns	-11,46 to 13,86
M LYM	0,4296	ns	0,9862	0,1854	1)			VH vs LD	-5,7	1,138	ns	-19,00 to 7,598
								VH vs MD	-7,8	1,651	ns	-20,34 to 4,737
								VH vs HD	-3,2	0,5867	ns	-17,68 to 11,28
M TPZ1	0,249	ns	1,549	0,2634	1)			VH vs LD	23,75	2,019	ns	-7,480 to 54,98
								VH vs MD	17,6	1,587	ns	-11,84 to 47,04
								VH vs HD	15,67	1,223	ns	-18,33 to 49,67

1) Group data size partly <5, test not possible

n.s.: not significant. Asterisks denote significance levels: *: p < 0,05, **: p < 0,01, ***: p < 0,001

Table A15: Statistics, blood analysis, females

Analysed parameter	One-way analysis of variance P	Sig	F	R sq.	Bartlett's test for equal variances B 's statistic (corr.)	P	Sig.	Dunnett's Multiple Comparison Test	Mean Diff	q	Sig.	95% CI of diff
F AP	0,1647	ns	1,935	0,2662	3,28	0,3505	ns	VH vs LD	-24	1,721	ns	-60,16 to 12,16
								VH vs MD	-31,2	2,237	ns	-67,36 to 4,956
								VH vs HD	-12	0,8604	ns	-48,16 to 24,16
F AST	0,1644	ns	1,936	0,2684	0,06872	0,9953	ns	VH vs LD	-9,2	1,38	ns	-26,48 to 8,082
								VH vs MD	-8,8	1,32	ns	-26,08 to 8,482
								VH vs HD	-16	2,4	ns	-33,28 to 1,282
F ALT	0,2518	ns	1,503	0,2198	4,47	0,215	ns	VH vs LD	7,6	1,25	ns	-8,160 to 23,36
								VH vs MD	9,6	1,579	ns	-6,160 to 25,36
								VH vs HD	-0,8	0,1316	ns	-16,56 to 14,96
F CHOL	0,8551	ns	0,2571	0,04599	2,543	0,4675	ns	VH vs LD	-0,08	0,4554	ns	-0,5354 to 0,3754
								VH vs MD	-0,056	0,3188	ns	-0,5114 to 0,3994
								VH vs HD	-0,152	0,8652	ns	-0,6074 to 0,3034
F HST	0,8896	ns	0,2076	0,03747	2,049	0,5623	ns	VH vs LD	-0,352	0,6432	ns	-1,771 to 1,067
								VH vs MD	-0,204	0,3728	ns	-1,623 to 1,215
								VH vs HD	-0,388	0,709	ns	-1,807 to 1,031
F GLUC	0,278	ns	1,404	0,2084	1,319	0,7245	ns	VH vs LD	1,468	1,926	ns	-0,5082 to 3,444
								VH vs MD	1,2	1,574	ns	-0,7762 to 3,176
								VH vs HD	0,936	1,228	ns	-1,040 to 2,912
F ELALP	0,3036	ns	1,317	0,198	0,6715	0,8799	ns	VH vs LD	2,32	1,607	ns	-1,423 to 6,063
								VH vs MD	2,44	1,69	ns	-1,303 to 6,183
								VH vs HD	0,92	0,6372	ns	-2,823 to 4,663
F ALBGR	0,0215	*	4,268	0,4445	0,9774	0,8067	ns	VH vs LD	0,54	2,595	*	0,0005565 to 1,079
								VH vs MD	0,34	1,634	ns	-0,1994 to 0,8794
								VH vs HD	-0,12	0,5767	ns	-0,6594 to 0,4194
F GLOBU	0,0112	*	5,13	0,4903	0,8424	0,8393	ns	VH vs LD	-2,466	2,742	*	-4,797 to -0,1349
								VH vs MD	-1,09	1,212	ns	-3,421 to 1,241
								VH vs HD	0,87	0,9675	ns	-1,461 to 3,201
F PROT	0,3669	ns	1,129	0,1747	6,658	0,0836	ns	VH vs LD	0	0	ns	-3,629 to 3,629
								VH vs MD	1,6	1,143	ns	-2,029 to 5,229
								VH vs HD	2	1,429	ns	-1,629 to 5,629
F NA	0,7829	ns	0,3597	0,06318	0,7405	0,8636	ns	VH vs LD	-0,6	0,4121	ns	-4,374 to 3,174
								VH vs MD	0,44	0,3022	ns	-3,334 to 4,214
								VH vs HD	0,84	0,577	ns	-2,934 to 4,614
F K	0,7328	ns	0,4322	0,07497	1,041	0,7915	ns	VH vs LD	-0,24	1,036	ns	-0,8408 to 0,3808
								VH vs MD	-0,212	0,9147	ns	-0,8128 to 0,3888
								VH vs HD	-0,128	0,5523	ns	-0,7288 to 0,4728
F CL	0,2238	ns	1,621	0,2331	0,9156	0,8217	ns	VH vs LD	-0,52	0,5042	ns	-3,194 to 2,154
								VH vs MD	-0,44	0,4266	ns	-3,114 to 2,234
								VH vs HD	1,48	1,435	ns	-1,194 to 4,154
F CA	0,3859	ns	1,079	0,1683	0,6057	0,8951	ns	VH vs LD	0,02	0,5143	ns	-0,08080 to 0,1208
								VH vs MD	0,068	1,749	ns	-0,03280 to 0,1688
								VH vs HD	0,032	0,823	ns	-0,06880 to 0,1328
F LEU	0,2705	ns	1,462	0,2523	1)			VH vs LD	0,52	0,4243	ns	-2,733 to 3,773
								VH vs MD	2,02	1,794	ns	-0,9682 to 5,008
								VH vs HD	1,72	1,621	ns	-1,097 to 4,537
F ERY	0,4592	ns	0,9184	0,1749	1)			VH vs LD	0,3093	1,186	ns	-0,3832 to 1,002
								VH vs MD	0,0085	0,03547	ns	-0,6277 to 0,6447
								VH vs HD	-0,12	0,5311	ns	-0,7198 to 0,4798
F HB	0,6025	ns	0,6402	0,1287				VH vs LD	2,333	0,7699	ns	-5,711 to 10,38
								VH vs MD	-2	0,7185	ns	-9,389 to 5,389
								VH vs HD	0,4	0,1524	ns	-6,567 to 7,367
F HKT	0,4039	ns	1,049	0,1949	1)			VH vs LD	0,01467	1,23	ns	-0,01699 to 0,04632
								VH vs MD	-0,002	0,1826	ns	-0,03108 to 0,02708
								VH vs HD	-0,006	0,5809	ns	-0,03342 to 0,02142
F MCV	0,9016	ns	0,1896	0,04193	1)			VH vs LD	-0,3333	0,2494	ns	-3,880 to 3,214
								VH vs MD	-0,55	0,4481	ns	-3,808 to 2,708
								VH vs HD	0,32	0,2765	ns	-2,752 to 3,392
F MCH	0,3652	ns	1,152	0,21	1)			VH vs LD	-0,3333	0,8143	ns	-1,420 to 0,7533
								VH vs MD	-0,25	0,6649	ns	-1,248 to 0,7481
								VH vs HD	0,32	0,9026	ns	-0,6211 to 1,261
F MCHC	0,4543	ns	0,9293	0,1766	1)			VH vs LD	-0,5	0,9713	ns	-1,867 to 0,8665
								VH vs MD	-0,125	0,2643	ns	-1,380 to 1,130
								VH vs HD	0,34	0,7626	ns	-0,8434 to 1,523
F THR	0,8104	ns	0,3206	0,06889	1)			VH vs LD	-33,07	0,6036	ns	-178,5 to 112,4
								VH vs MD	23,1	0,459	ns	-110,5 to 156,7
								VH vs HD	-1,4	0,02951	ns	-127,3 to 124,5
F RETIR	0,1894	ns	1,842	0,2983	1)			VH vs LD	-0,6	0,3144	ns	-5,665 to 4,465
								VH vs MD	1,65	0,9414	ns	-3,003 to 6,303
								VH vs HD	-2,4	1,452	ns	-6,787 to 1,987
F NEU	0,2767	ns	1,439	0,2493	1)			VH vs LD	2,667	1,231	ns	-3,086 to 8,419
								VH vs MD	-0,5	0,2512	ns	-5,784 to 4,784
								VH vs HD	-1,8	0,9591	ns	-6,782 to 3,182
F LYM	0,221	ns	1,676	0,2788	1)			VH vs LD	-4,4	1,672	ns	-11,38 to 2,584
								VH vs MD	-0,15	0,06206	ns	-6,566 to 6,266
								VH vs HD	1,4	0,6144	ns	-4,649 to 7,449
F TPZ1	0,4593	ns	0,9181	0,1748	1)			VH vs LD	45,2	1,589	ns	-30,30 to 120,7
								VH vs MD	18,7	0,7157	ns	-50,66 to 88,06
								VH vs HD	27,34	1,11	ns	-38,05 to 92,73

1) Group data size partly <5, test not possible

n.s.: not significant. Asterisks denote significance levels: *: p < 0,05, **: p < 0,01, ***: p < 0,001

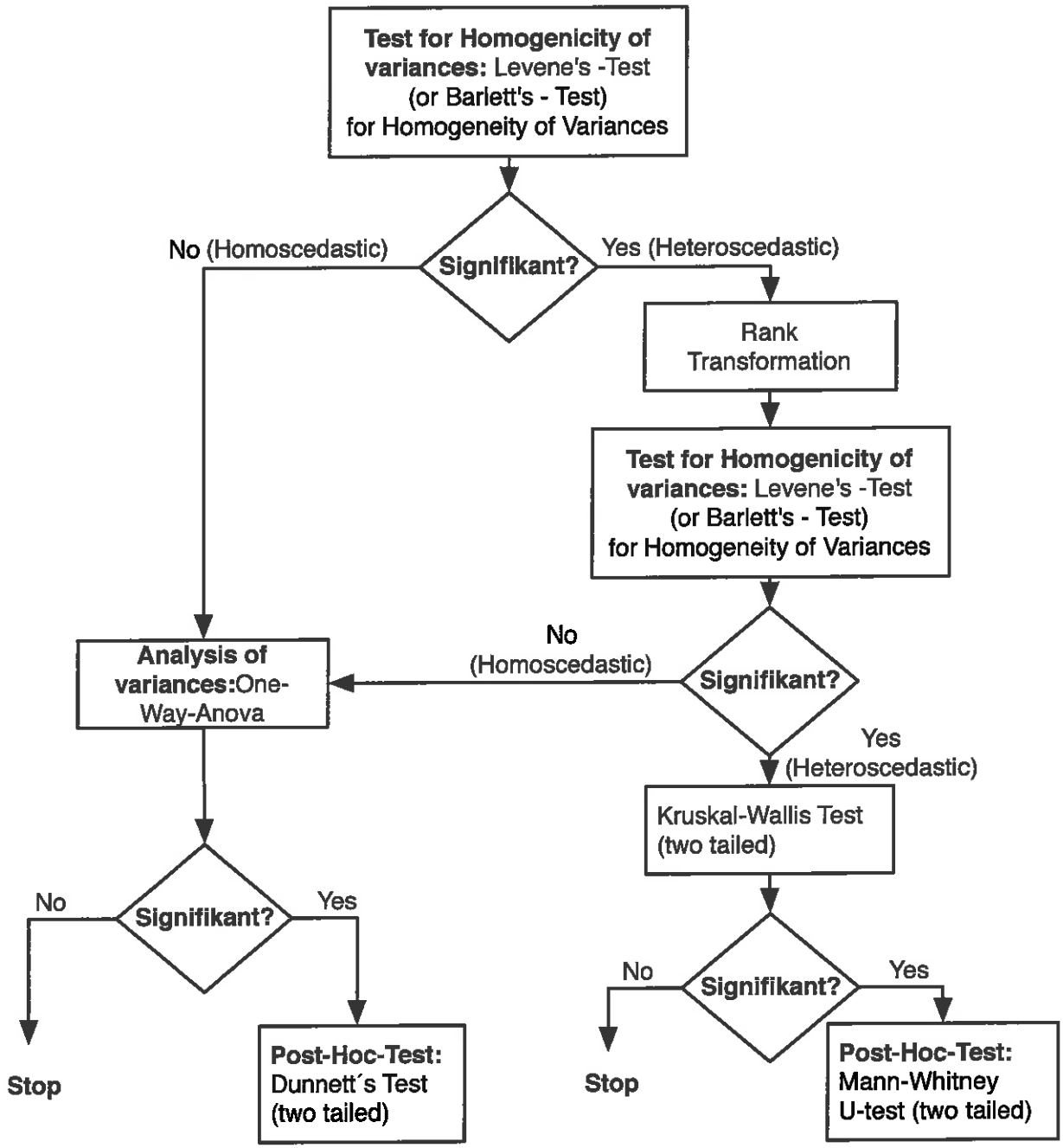
[redacted]

Table A16: Abbreviations used in this appendix

Abbreviation	Unit	Parameter
GS	g	Grip strength
Rel. GS	%	Grip strength, relative to body weight
BWS	-- or s	Beam walking score
DCS	–	Detailed clinical signs
F or FF	–	Indicator for female dose groups
M or MM	–	Indicator for male dose groups
AP	U/L	Alkaline phosphatase
AST	U/L	Aspartate transaminase or glutamic oxaloacetic transaminase (GOT)
ALT	U/L	Alanine transaminase or glutamic pyruvic transaminase (GPT)
GGT	U/L	Gamma glutamyl transferase
CHOL	mmol/L	Cholesterol
KREA	mmol/L	Creatinine
HST	mmol/L	Urea
GLUC	mmol/L	Glucose
ELALB	g/L	Albumin, total
ALBGR	–	Albumin-Globulin-Ratio
GLOBU	g/L	Globuline, total
PROT	g/L	Protein, total
NA	mmol/L	Sodium
K	mmol/L	Potassium
CL	mmol/L	Chloride
CA	mmol/L	Calcium
LEU	10^9/L	Leucocytes
ERY	10^3/L	Erythrocytes
HB	g/L	Haemoglobin
HKT	L/L	Haematokrit
MCV	fL	Mean corpuscular volume
MCH	pg	Mean corpuscular hemoglobin
MCHC	g/dl	Mean corpuscular hemoglobin, concentration
THR	10^9/L	Thrombocytes
RETIR	‰	Reticulocytes
RETIRA	/µL	Reticulocytes, absolute
NEU	%	Segmented neutrophile granulocytes
NEU2	%	Stab neutrophile granulocytes
LYM	%	Lymphocytes
MON	%	Monocytes
EOS	%	Eosinophils
BAS	%	Basophils
OTH	%	Other lycocytes
NEUA	/µL	Segmented neutrophile granulocytes, absolute
NEU2A	/µL	Stab neutrophile granulocytes, absolute
LYMA	/µL	Lymphocytes, absolute
MONA	/µL	Monocytes, absolute
EOSA	/µL	Eosinophils, absolute
BASA	/µL	Basophils, absolute
OTHA	/µL	Other lycocytes, absolute
TPZ1	s	Prothrombin time

n.s.: not significant. Asterisks denote significance levels: *: $p < 0,05$, **: $p < 0,01$, ***: $p < 0,001$

Table A17: Decision tree for statistical analysis (schematic)



Appendix B: Additional reports

[redacted]

[redacted]

Dose range finding study of [redacted] for a subacute toxicity test in rats

>> Summary Report [redacted]

- non GLP -

Final version: [redacted]

Sponsor: [redacted]

Test Facility: [redacted]

Study Monitor: [redacted]

Study Director: [redacted]

All numerical denotations in this study plan follow German conventions.

This summary report contains 5 pages.

[redacted]

[redacted]

SIGNATURES

STUDY DIRECTOR:

[redacted]

[redacted]

[redacted]

[redacted]

SUMMARY

Aim of the study:

The aim of this dose range study was to determine the suitable doses for an oral application of the test item to rats over a 28 days period.

Experimental model:

The test item was administered daily to three male and three female rats by oral gavage at escalating dose levels over a time period of 16 days, with a dose elevation every three days for the lower dosages (125, 250 and 500 mg/kg BW) in 5 ml/kg BW volume. The highest dose was applied for six days (1000 mg/kg BW). The individual dose volumes were calculated from the latest actual body weight data. The first day of application was designated as day 1. In case of signs of toxicity, the dose escalation would have been discontinued, with the dose remaining at the current level. The vehicle solution (sterilized tap water) was administered to three male and three female rats with an application volume of 5 ml/kg body weight as a vehicle control.

Test Item:

Identification
Containing (composition)

Molecular formula
Molecular weight
Purity
CAS No.
Batch No.
Batch production
Appearance
Storage conditions
Expiry date

Assessed parameters:

During the in-life phase, viability, general clinical signs, food and water consumption and the body weight were recorded.

At the end of the in-life phase, all animals were sacrificed and examined by gross necropsy. Weights of selected organs were recorded.

Results:

General clinical signs and motoric activity showed no remarkable abnormalities.

Body weight

The mean body weight gain of the male and female animals from all treated groups and the vehicle control group was within normal range for rats of this strain, gender and age, though a slight tendency of weight loss was presumably detectable in the last three days in both genders.

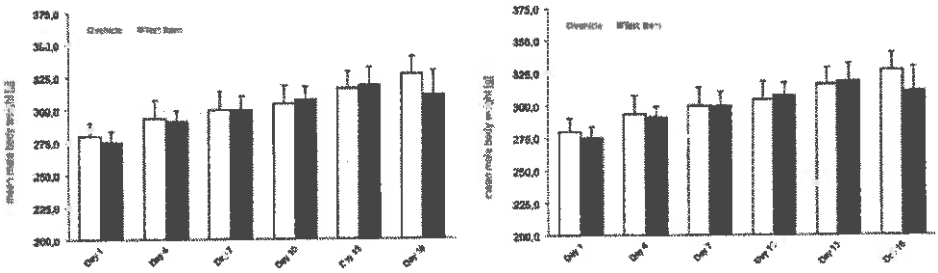


Figure 1 **Mean absolute body weight [g]** of the male (left) and the female (right) animals, sorted by groups (n=3) and treatment day. Means and standard deviations of each group are given.

Food consumption

The mean food consumption of the male and female animals from all treated groups and the vehicle control group was within normal range for rats of this strain and age, though a tendency of lower food consumption was presumably detectable in the male group on the last three days.

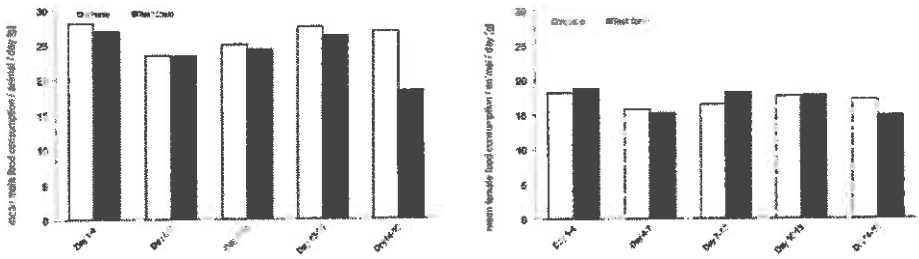


Figure 2 **Mean food consumption [g]** of the male (left) and the female (right) animals, per animal and day, sorted by experimental groups and treatment period (3 days).

Water consumption

The mean water consumption of the male and female animals from all treated groups and the vehicle control group was within normal range for rats of this strain and age.

[redacted]

[redacted]

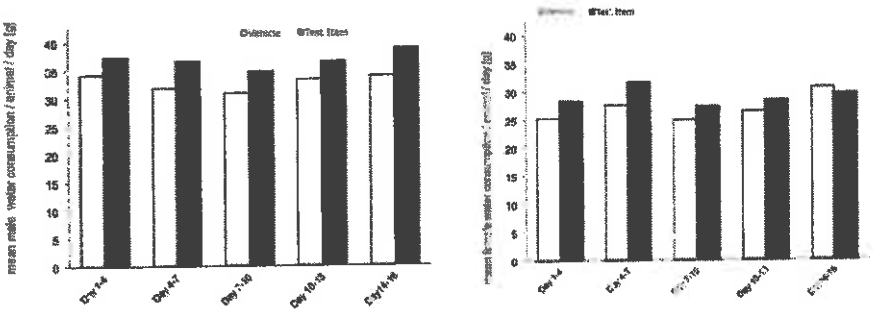


Figure 3 **Mean water consumption [g]** of the male (left) and the female (right) animals, per animal and day, sorted by experimental groups and treatment period (3 days).

Necropsy

At macroscopic examination, no remarkable pathological findings were noted for the test animals. The organ weight analysis showed normal results for the organs investigated.

Organ weight [g]													
Box#	Anim.#	Kidneys		Adrenals		Spleen	Liver	Heart	Brain	Testes		Epidydemis	
		left	right	left	right					left	right	left	right
E717	0	1,194	1,225	0,035	0,022	0,570	13,230	1,189	1,972	1,725	1,731	0,559	0,573
Male	1	1,229	1,287	0,043	0,038	0,572	14,941	1,122	2,001	1,687	1,668	0,448	0,471
Veh.	2	1,177	1,178	0,031	0,033	0,584	12,147	1,286	1,979	1,608	1,689	0,563	0,587
E718	0	1,178	1,221	0,041	0,039	0,476	13,463	1,110	2,019	1,783	1,751	0,513	0,502
Male	1	1,278	1,400	0,033	0,038	0,628	16,055	1,060	2,101	1,686	1,711	0,477	0,511
T. I.	2	1,514	1,617	0,048	0,047	0,542	11,169	1,192	1,977	1,664	1,610	0,579	0,683
E719	0	0,735	0,806	0,047	0,044	0,572	7,814	0,879	1,789				
Fem.	1	0,888	0,926	0,051	0,046	0,500	9,596	0,913	1,877				
Veh.	2	0,880	0,950	0,040	0,050	0,506	8,503	0,872	1,908				
E720	0	0,813	0,827	0,039	0,045	0,522	7,794	0,767	1,808				
Fem.	1	0,792	0,860	0,052	0,049	0,409	7,442	0,725	1,775				
T.I.	2	0,811	0,796	0,060	0,051	0,353	7,311	0,970	1,855				

Table 1 Organ weights of selected organs

Conclusion:

After a dose escalation study over 18 days a slight tendency of weight loss in the last three days was presumably detectable in both gender groups. A reduction of food consumption was possibly assessed in in the male treatment group. These mild effects can be tolerated for the 28 days main study especially if you take into account that no other alterations or effects were assessed. A daily oral administration of the test item [redacted] Wistar rats at a dose level of 111, 333 and 1000 mg/kg body weight over a time period of 28 days for the main study is recommended.

[redacted]

[redacted]

Histopathology report - Principal section (TPC)

PATHOLOGY REPORT [redacted]

TEST ITEM : [redacted]
TEST SYSTEM : RAT, 28 days, oral
SPONSOR [redacted]

PREPARED BY: [redacted]

[redacted]

PATHOLOGY REPORT

PAGE : I

TEST ITEM :
TEST SYSTEM : RAT, 28 days, oral
SPONSOR :

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PATHOLOGY REPORT PAGE : II

TEST ITEM :
TEST SYSTEM : RAT 28 days oral
SPONSOR :

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PATHOLOGY REPORT PAGE : 1/ 64

TEST ITEM :
TEST SYSTEM :
SPONSOR :

QUALITY ASSURANCE STATEMENT

This report was audited by the Quality Assurance Unit (QAU) of The respective dates are given below:

Date of QAU-audit	QAU control	Date of QAU-report
	microscopic examination	
	Raw Data 1. Draft Report	
	Final Report	

[redacted]

TEST ITEM : [redacted]
TEST SYSTEM : [redacted] 28 days, oral
SPONSOR [redacted]

PRINCIPAL INVESTIGATOR'S STATEMENT OC COMPLIANCE

The pathologic evaluation was performed according to:

- the principles of 'Good Laboratory Practice' as specified by national (German Chemicals Law, Annex 1, July 2, 2008) and international (OECD GLP Consensus document No. 13, Paris 2002) legislation.

The undersigned herewith confirms that the following histopathologic evaluation for this study was conducted by him in compliance with the methods described herein and the above mentioned 'Good Laboratory Practice' regulations and that this histopathology report fully and accurately reflects the results obtained in the slide assessment.

[redacted]

[redacted]

[redacted]

PATHOLOGY REPORT PAGE : 3/ 64
PRINCIPAL SECTION [redacted]

TEST ITEM : [redacted]
TEST SYSTEM : RAT, 28 days, oral
SPONSOR : [redacted]

SUMMARY

To evaluate possible toxic effects of the test item [redacted] pathomorphological examinations were performed on 20 male and 20 female Wistar rats, that were subjected to a 28-day toxicity study with the test item. The animals were allocated to 4 dose groups of 5 males and 5 females each and received the test item once daily by gavage at a dose level of 111, 333 or 1000 mg/kg body weight (groups 2, 3 and 4, respectively). The rats of group 1 received 5 mL of the vehicle (sterilised community tap water) per kg body weight and day instead and served as controls. At the end of the assigned study period, the rats were sacrificed and detailed necropsies performed. Histopathological examination was performed on all protocol designated organs from all animals of groups 1 (control) and 4 (1000 mg/kg body weight).

All rats examined survived the duration of the study.

At necropsy, no treatment-related findings were recorded.

No histopathologic findings were observed at microscopic examination, that are considered to be related to the treatment with the test item.

All microscopic findings recorded in various organs of animals of both dose groups examined (control and high dose) did not distinguish significantly treated rats of group 4 from control animals or the differences noted were regarded as random events. All these findings are considered to be spontaneous in nature and within the normal background pathology commonly seen in rats of this strain and age.

Under the conditions of this study, the repeated oral administration of the test item [redacted] by gavage to Wistar rats at a dose level of 1000 mg per kg body weight for a treatment period of 28 days did not produce any pathological evidence of a systemic toxicity of the test item.

[redacted]

PATHOLOGY REPORT
PRINCIPAL SECTION

PAGE : 4/ 64

[redacted]

TEST ITEM : [redacted]
TEST SYSTEM : RAT, 28 days, oral
SPONSOR : [redacted]

METHODS

Group Design for Pathological Evaluation

Dose Group	Pathdata Group	Test item* (mg/kg b.w./day)	Number of Rats** Males/Females	Animal numbers Males	Females
1	01	0 (Vehicle control)	5/5	11-794-0, 11-794-1, 11-794-2, 11-794-3, 11-794-4,	11-798-0, 11-798-1, 11-798-2, 11-798-3, 11-798-4
2	02	111 (low dose)	5/5	11-793-0, 11-793-1, 11-793-2, 11-793-3, 11-793-4,	11-797-0, 11-797-1, 11-797-2, 11-794-3, 11-797-4
3	03	333 (medium dose)	5/5	11-792-0, 11-792-1, 11-792-2, 11-792-3, 11-792-4,	11-796-0, 11-796-1, 11-796-2, 11-796-3, 11-796-4
4	04	1000 (high dose)	5/5	11-791-0, 11-791-1, 11-791-2, 11-791-3, 11-791-4,	11-795-0, 11-795-1, 11-795-2, 11-795-3, 11-795-4

* [redacted]
** Strain: Wistar Han (IGS), (Source: Charles River, Sandhofer Weg 7, D-97633 Sulzfeld, Germany)

Administration of the Test Item

The in-life part of the study was performed at [redacted] The test item [redacted] was administered orally by gavage once daily for a treatment period of 28 days. The rats of group 01 received 5 mL/kg body weight of the vehicle (sterilised community tap water) once daily instead and served as control rats.

[redacted]

PATHOLOGY REPORT
PRINCIPAL SECTION

PAGE : 5/ 64

TEST ITEM : [redacted]
TEST SYSTEM : [redacted]
SPONSOR : [redacted]

METHODS

Necropsy and Histopathology

At the end of the assigned study period (test day 29), the rats were sacrificed by carbon dioxide asphyxiation and subjected to a detailed postmortem examination by [redacted]. All organs were examined at necropsy and all macroscopic findings recorded. Macroscopic findings are given for each rat in full descriptive terms in the "Individual Animal Data - Text of Gross and Microscopic Findings".

Representative tissue samples of following organs of animals of all groups were preserved in 4% neutral buffered formaldehyde solution:

Adrenal glands, bone (sternum), bone marrow (sternum), brain (cerebrum, cerebellum, pons/brainstem), epididymides, eyes with optic nerves, oesophagus, heart, intestine -small (duodenum, jejunum, ileum, with Peyer's patches), intestine -large (caecum, colon, rectum), kidneys, liver, lungs, lymph nodes (axillary, mesenteric), ovaries, peripheral nerve (sciatic), prostate gland, seminal vesicles, skeletal muscle, spinal cord, spleen, stomach, testes, thymus, thyroid gland (incl. parathyroid glands), trachea, urinary bladder, uterus incl. cervix, vagina and gross lesions.

Histotechnique was performed by [redacted] Samples of following organs of all rats of groups 01 and 04 were trimmed, processed, embedded in paraffin wax and sectioned at a nominal thickness of about 5 µm. All sections [redacted] were shipped to [redacted] for histopathologic examination. [redacted] by the undersigned pathologist [redacted] by light microscope except where indicated in parentheses:

Adrenal glands (2), bone (sternum), bone marrow (sternum), brain (cerebrum, cerebellum, pons/brainstem) (3), epididymides (2), eyes (2), heart, intestine -large (caecum, colon, rectum) (3), intestine -small (duodenum, jejunum, ileum) (3), kidneys (2), larynx, liver (2), lungs, lymph nodes (axillary, mesenteric) (2), oesophagus, optic nerves (2), ovaries (2), parathyroid glands (2), Peyer's patches, prostate gland, sciatic nerve, seminal vesicles (2), skeletal muscle, spinal cord (3), spleen, stomach (2), testes (2), thymus, thyroid gland (2), trachea, urinary bladder, uterus (both horns, corpus with cervix) (3) and vagina. Additional findings in nonprotocol organs present on slides by chance were only recorded, if they were of pathological significance.

[redacted]

PATHOLOGY REPORT
PRINCIPAL SECTION

PAGE : 6/ 64

TEST ITEM [redacted]
TEST SYSTEM [redacted]
SPONSOR [redacted]

METHODS

Data compilation

The animal heading data and necropsy findings recorded by [redacted] at postmortem examination were taken from the postmortem records, translated faithfully into English and entered manually into [redacted] current version, under [redacted] is a registered trademark of Pathology Data Systems, Inc.). Microscopic findings are recorded by the undersigned pathologist during histopathological examination using on-line data input into the pathology computer system.

All microscopic observations are presented for each rat in the "Table of Individual Microscopic Findings" as well as in full descriptive terms in the "Individual Animal Data - Text of Gross and Microscopic Findings". The incidence of microscopic findings is also presented in tabular form. Incidence tables were created by the PathData software. Histologic alterations were described, wherever possible, according to their distribution, severity and morphologic character. Severity scores were assigned as given under "Explanation of Codes and Symbols".

The slides were evaluated during the period [redacted]

Quality Assurance Review

A review of the raw data and the pathology report was conducted by [redacted] The correspondence of the report data and the raw data was confirmed in a Quality Assurance Statement.

Archive

For archiving purposes, raw data incl. a CD-ROM containing the electronic study data of the pathology computer system as well as the microscopic slides will be returned to [redacted]

[redacted]

TEST ITEM [redacted]
TEST SYSTEM : RAT, 28 days, oral
SPONSOR : [redacted]

RESULTS

Mortality

All animals of all groups survived the duration of the study.

Macroscopic Findings

At necropsy, no treatment-related macroscopic alterations were observed in the animals of this study.

Microscopic Findings

At histopathologic examination, a small number of microscopic findings was recorded in the organs examined in this study. These findings are also described in detail in the "Individual Animal Data - Text of Gross and Microscopic Findings". The type, incidence and severity of all microscopic findings noted did not indicate a relationship to the treatment with the test item.

All alterations were regarded to be spontaneous in nature and within the normal background pathology commonly seen in rats of this strain and age.

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PRINCIPAL SECTION

TEST ITEM : [redacted]
TEST SYSTEM : RAT, 28 days, oral
SPONSOR : [redacted]

CONCLUSIONS

All animals survived the duration of the study of the repeated oral administration of the test item [redacted] to Wistar rats for a treatment period of 28 days at dose levels of 0 (group 1), 111 (group 2), 333 (group 3) or 1000 (group 4) mg/kg body weight/day.

At necropsy, no treatment-related findings were recorded.

There were also no microscopic findings recorded in the examined high dose animals of group 4 that are considered to be related to the treatment with test item.

All microscopic findings recorded in various organs of animals of both dose groups examined (control and high dose) did not distinguish significantly treated rats of group 4 from control animals or the differences noted were regarded as random events. All these findings are considered to be spontaneous in nature and within the normal background pathology commonly seen in rats of this strain and age.

Under the conditions of this study, the repeated oral administration of the test item [redacted] by gavage to Wistar rats at a dose level of 1000 mg per kg body weight for a treatment period of 28 days did not produce any pathological evidence of a systemic toxicity of the test item.

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TEST ITEM : [redacted]
TEST SYSTEM : RAT, 28 days, oral
SPONSOR : [redacted]

EXPLANATION OF CODES AND SYMBOLS

CODES AND SYMBOLS USED AT ANIMAL LEVEL:

M = Male animal
F = Female animal
K0 = Terminal sacrifice group

CODES AND SYMBOLS USED AT ORGAN LEVEL:

G = Gross observation checked off histologically
! = Gross observat.not checked off histologically
* = Comment in text of individual animal data
0 = Tissue not present for histologic examination
' = Histologic examination not required
+ = Organ examined, findings present
- = Organ examined, no pathologic findings noted (AOFT only)
(= Only one of paired organs examined/present

CODES AND SYMBOLS USED AT FINDING LEVEL:

GRADE 1 = Minimal / very few / very small
GRADE 2 = Slight / few / small
GRADE 3 = Moderate / moderate number / moderate size
P = Finding present, severity not scored
(= Finding unilateral in paired organs

PATHOLOGY REPORT
SUMMARY TABLES

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[redacted]

TEST ITEM : [redacted]
TEST SYSTEM : [redacted] oral
SPONSOR [redacted]

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0)

Sex		Males				Females			
Dose Group No. Animals per Dose Group.		1 5	2 5	3 5	4 5	1 5	2 5	3 5	4 5
ADRENAL GLANDS	No.Examined	5	-	-	5	5	-	-	5
BONE (STERNUM)	No.Examined	5	-	-	5	5	-	-	5
BONE MARROW -STERNUM	No.Examined	5	-	-	5	5	-	-	5
BRAIN	No.Examined	5	-	-	5	5	-	-	5
EPIDIDYMIDES	No.Examined	5	-	-	5	-	-	-	-
EYES	No.Examined	5	-	-	5	5	-	-	5
- posttraumatic change		- - -	- - -	- - -	3 1 2	1 1 -	- - -	- - -	2 1 1
	Grade 1 Grade 2								
OPTIC NERVES	No.Examined	3	-	-	3	3	-	-	1
HEART	No.Examined	5	-	-	5	5	-	-	5
- mononuclear cell infiltrate(s)		1 1	- -	- -	1 1	- -	- -	- -	- -
	Grade 1								
- fibrosis		1 1	- -	- -	- -	- -	- -	- -	- -
	Grade 1								
INTESTINE, LARGE	No.Examined	5	-	-	5	5	-	-	5
INTESTINE, SMALL	No.Examined	5	-	-	5	5	-	-	5
PEYER'S PATCHES	No.Examined	4	-	-	4	3	-	-	5
KIDNEYS	No.Examined	5	-	-	5	5	-	-	5
- mononuclear cell infiltrate(s)		3 3	- -	- -	1 1	- -	- -	- -	- -
	Grade 1								
- pelvic dilation		- -	- -	- -	1 1	- -	- -	- -	- -
	Grade 1								
- tubular cast(s)		1 1	- -	- -	- -	1 1	- -	- -	1 1
	Grade 1								
LARYNX	No.Examined	5	-	-	5	5	-	-	5
- mononuclear cell infiltrate(s)		2 2	- -	- -	3 3	1 1	- -	- -	2 2
	Grade 1								
- glandular dilation		3 - 3	- - -	- - -	4 3 1	3 2 1	- - -	- - -	3 - 3
	Grade 1 Grade 2								
LIVER	No.Examined	5	-	-	5	5	-	-	5
- inflammatory cell infiltrate(s)		1	-	-	2	-	-	-	1
	Grade 1	1	-	-	2	-	-	-	1
- mononuclear cell infiltrate(s)		4 4	- -	- -	2 2	2 2	- -	- -	- -
	Grade 1								

[redacted]

PATHOLOGY REPORT
SUMMARY TABLES

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[redacted]

TEST ITEM : [redacted]
TEST SYSTEM : RAT, 28 days, oral
SPONSOR : [redacted]

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0)

Sex	Males				Females			
Dose Group No. Animals per Dose Group	1 5	2 5	3 5	4 5	1 5	2 5	3 5	4 5
LUNGS No.Examined	5	-	-	5	5	-	-	5
- granulocytic cell infiltrate(s)	1	-	-	1	-	-	-	2
Grade 1	1	-	-	1	-	-	-	2
- mononuclear cell infiltrate(s)	1	-	-	-	-	-	-	-
Grade 1	1	-	-	-	-	-	-	-
- alveolar macrophages	-	-	-	-	1	-	-	-
Grade 1	-	-	-	-	1	-	-	-
AXILLARY LYMPH NODES No.Examined	5	-	-	5	5	-	-	5
- histiocytosis	5	-	-	5	5	-	-	4
Grade 1	1	-	-	1	2	-	-	-
Grade 2	4	-	-	4	3	-	-	4
- germinal center reaction	5	-	-	4	3	-	-	-
Grade 1	5	-	-	4	3	-	-	-
- plasmocytosis	2	-	-	1	-	-	-	-
Grade 1	2	-	-	-	-	-	-	-
Grade 3	-	-	-	1	-	-	-	-
- pigment	1	-	-	-	-	-	-	-
Grade 1	1	-	-	-	-	-	-	-
MESENT. LYMPH NODE No.Examined	5	-	-	5	5	-	-	5
- histiocytosis	5	-	-	5	5	-	-	5
Grade 1	2	-	-	2	2	-	-	-
Grade 2	1	-	-	3	3	-	-	4
Grade 3	2	-	-	-	-	-	-	1
- germinal center reaction	3	-	-	2	4	-	-	5
Grade 1	2	-	-	2	4	-	-	4
Grade 2	1	-	-	-	-	-	-	1
- plasmocytosis	-	-	-	1	-	-	-	1
Grade 1	-	-	-	-	-	-	-	1
Grade 2	-	-	-	1	-	-	-	-
- haemorrhage/blood resorption	1	-	-	-	-	-	-	-
Grade 1	1	-	-	-	-	-	-	-
- pigment	1	-	-	-	-	-	-	-
Grade 1	1	-	-	-	-	-	-	-
OESOPHAGUS No.Examined	5	-	-	5	5	-	-	5
OVARIES No.Examined	-	-	-	-	5	-	-	5
- tubular structure(s)	-	-	-	-	3	-	-	2
PARATHYROID GLANDS No.Examined	2	-	-	3	3	-	-	4
PROSTATE No.Examined	5	-	-	5	-	-	-	-
- mononuclear cell infiltrate(s)	2	-	-	1	-	-	-	-
Grade 1	1	-	-	1	-	-	-	-
Grade 2	1	-	-	-	-	-	-	-

[redacted]

PATHOLOGY REPORT
SUMMARY TABLES

[redacted]

TEST ITEM : [redacted]
TEST SYSTEM : RAT, 28 days, oral
SPONSOR : [redacted]

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0)

Sex		Males				Females			
Dose Group No. Animals per Dose Group		1 5	2 5	3 5	4 5	1 5	2 5	3 5	4 5
SCIATIC NERVE	No.Examined	5	-	-	5	5	-	-	5
SEMINAL VESICLES	No.Examined	5	-	-	5	-	-	-	-
SKELETAL MUSCLE	No.Examined	5	-	-	5	5	-	-	5
SPINAL CORD	No.Examined	5	-	-	5	5	-	-	5
SPLEEN	No.Examined	5	-	-	5	5	-	-	5
- pigment		4	-	-	1	5	-	-	5
	Grade 1	4	-	-	1	5	-	-	5
- extramedullary haematopoiesis		2	-	-	3	1	-	-	-
	Grade 1	2	-	-	3	1	-	-	-
STOMACH	No.Examined	5	-	-	5	5	-	-	5
- mononuclear cell infiltrate(s)		1	-	-	1	-	-	-	-
	Grade 1	1	-	-	1	-	-	-	-
- epithelial cell vacuolation		-	-	-	3	1	-	-	3
	Grade 1	-	-	-	3	1	-	-	1
	Grade 2	-	-	-	-	-	-	-	2
TESTES	No.Examined	5	-	-	5	-	-	-	-
THYMUS	No.Examined	5	-	-	5	5	-	-	5
- haemorrhage		2	-	-	2	1	-	-	1
	Grade 1	2	-	-	2	1	-	-	1
- tubular structure(s)		-	-	-	1	2	-	-	-
	Grade 1	-	-	-	1	1	-	-	-
	Grade 2	-	-	-	-	1	-	-	-
THYROID GLAND	No.Examined	5	-	-	5	5	-	-	5
- lymphoid follicle		-	-	-	1	-	-	-	-
	Grade 1	-	-	-	1	-	-	-	-
TRACHEA	No.Examined	5	-	-	5	5	-	-	5
- mononuclear cell infiltrate(s)		1	-	-	-	1	-	-	-
	Grade 1	1	-	-	-	1	-	-	-
URINARY BLADDER	No.Examined	5	-	-	5	5	-	-	5
UTERUS	No.Examined	-	-	-	-	5	-	-	5
- dilation		-	-	-	-	2	-	-	1
	Grade 2	-	-	-	-	2	-	-	1
- cyst		-	-	-	-	1	-	-	-
	Grade 1	-	-	-	-	1	-	-	-
VAGINA	No.Examined	-	-	-	-	5	-	-	5

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INDIVIDUAL ANIMAL DATA

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[redacted]

TEST ITEM : [redacted]
TEST SYSTEM : [redacted] oral
SPONSOR : [redacted]

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 1, Vehicle

ANIMAL NUMBER :	11-7 94-0 MK0	11-7 94-1 MK0	11-7 94-2 MK0	11-7 94-3 MK0	11-7 94-4 MK0	11-7 98-0 FK0	11-7 98-1 FK0	11-7 98-2 FK0	11-7 98-3 FK0	11-7 98-4 FK0
ADRENAL GLANDS	-	-	-	-	-	-	-	-	-	-
BONE (STERNUM)	-	-	-	-	-	-	-	-	-	-
BONE MARROW -STERNUM	-*	-	-	-	-	-	-	-	-	-
BRAIN	-	-	-	-	-	-	-	-	-	-
EPIDIDYMIDES	-	-	-	-	-					
EYES	-	-	-	-	(-	-	+	-	(-	-
- posttraumatic change	.	.	.	.	.	.	(1.	.	.	.
OPTIC NERVES	-	(-	0	0	(-	0	0	(-	(-	(-
HEART	-	-	-	-	+	-	-	-	-	-
- mononuclear infilt.	.	.	.	.	1.	.	.	.	.	.
- fibrosis	.	.	.	.	1.	.	.	.	.	.
INTESTINE, LARGE	-	-	-	-	-	-	-	-	-	-
INTESTINE, SMALL	-	-	-	-	-	-	-	-	-	-
PEYER'S PATCHES	-	-	0	-	-	-	-	0	0	-
KIDNEYS	+	+	+	+	-	-	+	-	-	-
- mononuclear infilt.	.	(1.	(1.	(1.	.	.	.	.	.	.
- tubular cast(s)	(1.	.	.	.	.	.	(1.	.	.	.
LARYNX	+	-	+	+	+	+	-	+	+	+
- mononuclear infilt.	.	.	1.	.	1.	.	.	1.	.	.
- glandular dilation	2.	.	.	2.	2.	1.	.	.	2.	1.
LIVER	-	+	+	+	+	+	-	-	+	-
- inflammatory infilt.	.	.	.	.	1.	.	.	.	.	.
- mononuclear infilt.	.	1.	1.	1.	1.	1.	.	.	1.	.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

[redacted]

TEST ITEM : [redacted]
TEST SYSTEM : RAT 28 days, oral
SPONSOR : [redacted]

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 1, Vehicle

ANIMAL NUMBER :	11-7 94-0 MK0	11-7 94-1 MK0	11-7 94-2 MK0	11-7 94-3 MK0	11-7 94-4 MK0	11-7 98-0 FK0	11-7 98-1 FK0	11-7 98-2 FK0	11-7 98-3 FK0	11-7 98-4 FK0
LUNGS	-	-	+	-	+	-	-	+	-	-
- granulocytic infilt.	.	.	.	.	1.	.	.	.	.	.
- mononuclear infilt.	.	.	1.	.	.	.	.	.	.	.
- alveolar macrophages	.	.	.	.	.	.	.	1.	.	.
LYMPH NODE	.	OG	.	.	.	.	.	.	.	.
AXILLARY LYMPH NODE	+	+	+	+	+	+	+	+	+	+
- histiocytosis	1.	2.	2.	2.	2.	1.	2.	2.	1.	2.
- germinal center reac	1.	1.	1.	1.	1.	.	1.	.	1.	1.
- plasmocytosis	.	.	1.	1.	.	.	.	.	.	.
- pigment	.	.	1.	.	.	.	.	.	.	.
MESENT. LYMPH NODE	+	+	+	+	+	+	+	+	+	+
- histiocytosis	1.	3.	3.	1.	2.	2.	2.	1.	2.	1.
- germinal center reac	1.	2.	.	.	1.	1.	1.	.	1.	1.
- haemorrhage	1.	.	.	.	.	.	.	.	.	.
- pigment	.	.	1.	.	.	.	.	.	.	.
OESOPHAGUS	-	-	-	-	-	-	-	-	-	-
OVARIES						+	+	-	+	-
- tubular structure(s)						(P.	(P.	.	(P.	.
PARATHYROID GLANDS	(-	0	0	0	(-	(-	(-	0	(-	0
PROSTATE	-	+	-	+	-					
- mononuclear infilt.	.	2.	.	1.	.					
SCIATIC NERVE	-	-	-	-	-	-	-	-	-	-
SEMINAL VESICLES	-	-	(-	-	-					
SKELETAL MUSCLE	-	-	-	-	-	-	-	-	-	-
SPINAL CORD	-	-	-	-	-	-	-	-*	-	-

[redacted]

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

[redacted]

TEST ITEM : [redacted]
TEST SYSTEM : [redacted]
SPONSOR : [redacted]

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 1, Vehicle

ANIMAL NUMBER :	11-7 94-0 MK0	11-7 94-1 MK0	11-7 94-2 MK0	11-7 94-3 MK0	11-7 94-4 MK0	11-7 98-0 FK0	11-7 98-1 FK0	11-7 98-2 FK0	11-7 98-3 FK0	11-7 98-4 FK0
SPLEEN	+	+	+	+	+	+	+	+	+	+
- pigment	1.	1.	1.	1.	.	1.	1.	1.	1.	1.
- extr. haematopoiesis	.	.	1.	.	1.	.	1.	.	.	.
STOMACH	-	+	-	-	-	-	-	-	-	+
- mononuclear infilt.	.	1.	.	.	.	.	.	.	.	.
- epithel. vacuolation	.	.	.	.	.	.	.	.	.	1.
TESTES	-	-	-	-	-					
THYMUS	-	-	+	+	-	+	-	-	-	+
- haemorrhage	.	.	1.	1.	.	1.	.	.	.	.
- tubular structure(s)	.	.	.	.	.	1.	.	.	.	2.
THYROID GLAND	-	-	-	-	-	-	-	-	-	-
TRACHEA	-	-	+	-	-	-	-	-	+	-
- mononuclear infilt.	.	.	1.	.	.	.	.	.	1.	.
URINARY BLADDER	-	-	-	-	-	-	-	-	-	-
UTERUS						-	+	-	+	+
- dilation						.	2.	.	2.	.
- cyst						.	.	.	.	1.
VAGINA						-	-	-	-	-

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

TEST ITEM :
TEST SYSTEM : RAT, 28 days, oral
SPONSOR :

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 2, low dose (111 mg/kg)

ANIMAL NUMBER :	11-7 93-0 MK0	11-7 93-1 MK0	11-7 93-2 MK0	11-7 93-3 MK0	11-7 93-4 MK0	11-7 97-0 FK0	11-7 97-1 FK0	11-7 97-2 FK0	11-7 97-3 FK0	11-7 97-4 FK0
THYMUS	'	'	'	'	'	'	'	'	'	'!

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INDIVIDUAL ANIMAL DATA

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TEST ITEM :
TEST SYSTEM : RAT, 28 days, oral
SPONSOR :

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 4, high dose (1000 mg/kg)

ANIMAL NUMBER :	11-7 91-0 MK0	11-7 91-1 MK0	11-7 91-2 MK0	11-7 91-3 MK0	11-7 91-4 MK0	11-7 95-0 FK0	11-7 95-1 FK0	11-7 95-2 FK0	11-7 95-3 FK0	11-7 95-4 FK0
ADRENAL GLANDS	-*	-	-	-	-	-	-*	-	-	-
BONE (STERNUM)	-	-	-	-	-	-	-	-	-	-
BONE MARROW -STERNUM	-	-	-	-	-	-	-	-	-	-
BRAIN	-	-	-	-	-	-	-	-	-	-
EPIDIDYMIDES	-	-	-	-	-					
EYES	+	-	+	+	-	-	-	+	-	+
- posttraumatic change	(2.	.	(2.	(1.	.	.	.	(1.	.	(2.
OPTIC NERVES	(-	(-	0	0	-	-	0	0	0	0
HEART	-	-	-	-	+	-	-	-	-	-
- mononuclear infilt.	.	.	.	.	1.	.	.	.	.	.
INTESTINE, LARGE	-	-*	-	-	-	-	-	-	-	-
INTESTINE, SMALL	-	-	-	-	-	-	-*	-	-	-
PEYER'S PATCHES	-	-	-	-	0	-	-	-	-	-
KIDNEYS	-	+	+	-	-	-	-	+	-	-
- mononuclear infilt.	.	.	(1.	.	.	.	.	.	.	.
- pelvic dilation	.	(1.	.	.	.	.	.	.	.	.
- tubular cast(s)	.	.	.	.	.	.	.	(1.	.	.
LARYNX	+	+	+	+	+	+	+	+	+	+
- mononuclear infilt.	.	1.	1.	1.	.	1.	.	.	1.	.
- glandular dilation	1.	2.	.	1.	1.	.	2.	2.	.	2.
LIVER	+	+	+	-	-	+	-	-	-	-
- inflammatory infilt.	1.	.	1.	.	.	1.	.	.	.	.
- mononuclear infilt.	1.	1.	.	.	.	.	.	.	.	.
LUNGS	-	-	-	-	+	-	+	-	+	-
- granulocytic infilt.	.	.	.	.	1.	.	1.	.	1.	.

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

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[redacted]

TEST ITEM : [redacted]
TEST SYSTEM : RAT, 28 days, oral
SPONSOR : [redacted]

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 4, high dose (1000 mg/kg)

ANIMAL NUMBER :	11-7 91-0 MK0	11-7 91-1 MK0	11-7 91-2 MK0	11-7 91-3 MK0	11-7 91-4 MK0	11-7 95-0 FK0	11-7 95-1 FK0	11-7 95-2 FK0	11-7 95-3 FK0	11-7 95-4 FK0
AXILLARY LYMPH NODE	+	+	+	+	+	+	+	+	-*	+
- histiocytosis	1.	2.	2.	2.	2.	2.	2.	2.	.	2.
- germinal center reac	1.	1.	1.	1.	.	.	.	.	.	.
- plasmocytosis	3.	.	.	.	.	.	.	.	.	.
MESENT. LYMPH NODE	+	+	+	+	+	+	+	+	+	+
- histiocytosis	2.	1.	1.	2.	2.	2.	2.	2.	3.	2.
- germinal center reac	.	1.	1.	.	.	2.	1.	1.	1.	1.
- plasmocytosis	.	.	.	.	2.	.	1.	.	.	.
OESOPHAGUS	-	-	-	-	-	-	-	-	-	-
OVARIES						+	-	+	-	-
- tubular structure(s)						(P.	.	(P.	.	.
PARATHYROID GLANDS	0	-	(-	0	(-	0	(-	(-	(-	(-
PROSTATE	-	-	-	-	+					
- mononuclear infilt.	.	.	.	.	1.					
SCIATIC NERVE	-	-	-	-	-	-	-	-	-	-
SEMINAL VESICLES	-	(-	(-	-	-					
SKELETAL MUSCLE	-	-	-	-	-	-	-	-	-	-
SPINAL CORD	-	-	-	-	-	-	-	-	-	-
SPLEEN	+	+	+	+	-	+	+	+	+	+
- pigment	.	1.	.	.	.	1.	1.	1.	1.	1.
- extr. haematopoiesis	1.	.	1.	1.	.	.	.	.	.	.
STOMACH	-	+	+	-	+	-	+	-	+	+
- mononuclear infilt.	.	1.	.	.	.	.	.	.	.	.
- epithel. vacuolation	.	1.	1.	.	1.	.	2.	.	1.	2.
TESTES	-	-	-	-	-					

PATHOLOGY REPORT
INDIVIDUAL ANIMAL DATA

[redacted]

TEST ITEM [redacted]
TEST SYSTEM : RAT, 28 days, oral
SPONSOR : [redacted]

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 4, high dose (1000 mg/kg)

ANIMAL NUMBER :	11-7 91-0 MK0	11-7 91-1 MK0	11-7 91-2 MK0	11-7 91-3 MK0	11-7 91-4 MK0	11-7 95-0 FK0	11-7 95-1 FK0	11-7 95-2 FK0	11-7 95-3 FK0	11-7 95-4 FK0
THYMUS	-	+	-	-	+	+	-	-	-	-
- haemorrhage	.	1.	.	.	1.	1.	.	.	.	.
- tubular structure(s)	.	1.	.	.	.	.	.	.	.	.
THYROID GLAND	-	-	+	-	-	-	-	-	-	-
- lymphoid follicle	.	.	1.	.	.	.	.	.	.	.
TRACHEA	-	-	-	-	-	-	-	-	-	-
URINARY BLADDER	-	-	-	-	-	-	-	-	-	-
UTERUS						-	+	-	-	-
- dilation						.	2.	.	.	.
VAGINA						-	-	-	-	-

[redacted]

Summary report: Haematology and clinical biochemistry

S. 01/01

To whom it may concern,

The external contract laboratory provided the haemogram (EDTA-blood) data, the blood biochemistry data and the blood clotting times (heparin-blood) from the samples listed in table 1. The samples were individually labelled at the time of exchange specified in detail in the according Test Item Submission Form (TISF) o

Table 1

Blood samples Wistar ha	Blood samples Wistar han
11/783/0-4 (5 EDTA-, 5 heparin samples)	11/791/0-4 (5 EDTA-, 5 heparin samples)
11/784/0-4 (5 EDTA-, 5 heparin samples)	11/792/0-4 (5 EDTA-, 5 heparin samples)
11/785/0-4 (5 EDTA-, 5 heparin samples)	11/793/0-4 (5 EDTA-, 5 heparin samples)
11/786/0-4 (5 EDTA-, 5 heparin samples)	11/794/0-4 (5 EDTA-, 5 heparin samples)
11/787/0-4 (5 EDTA-, 5 heparin samples)	11/795/0-4 (5 EDTA-, 5 heparin samples)
11/788/0-4 (4 EDTA-, 4 heparin samples)	11/796/0-4 (5 EDTA-, 5 heparin samples)
11/789/0-4 (5 EDTA-, 5 heparin samples)	11/797/0-4 (5 EDTA-, 5 heparin samples)
11/790/0-4 (5 EDTA-, 5 heparin samples)	11/798/0-4 (5 EDTA-, 5 heparin samples)

The courier service picked up all samples on the day of blood collection at the test facility ood analysis was performed 8 h after bleeding at the latest. After analysis, surplus blood was disposed of Data exchange took place on standardised, signed PC-printout-sheets.

QUALITY- STATEMENT

The blood analysis was performed according to the respective internal SOPs of ere were no deviations from the standard procedures during the course of this analysis.

Appendix C: Study plan

[redacted]

Toxicity Study of [redacted]

28-days Oral Toxicity Test in Wistar Rats

>> Study Plan [redacted]

- GLP -

Final version [redacted]

Sponsor:
[redacted]

Test facility:
[redacted]

Study Monitor:
[redacted]

Study Director:
[redacted]

All numerical denotations in this study plan abide German regulations.
This study plan contains 19 pages without appendices.

[redacted]

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[redacted]

SIGNATURES

STUDY DIRECTOR:

TEST FACILITY MANAGER:

QUALITY ASSURANCE:

STUDY MONITOR:

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SIGNATURES

PRINCIPAL INVESTIGATOR 1:

PRINCIPAL INVESTIGATOR 2:

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ABREVATIONS

BW	Body weight
CW	Calendar week
DRF	Dose Range Finding
PI	Principal Investigator
SOP	Standard Operating Procedure

[redacted]

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[redacted]

SPF Specific Pathogen Free

1 Preface

1.1 Identification

Title: **Toxicity study of**
28-days Oral Toxicity Test in Wistar Rats

Study number:

Sponsor:

Test Facility:

Princ. Investigator 1:
(Haematology)

Princ. Investigator 2:
(Histopathology)

1.2 Responsibilities

Study Director:

Deputy Study Director:

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Test Facility Manager: [redacted]

Quality Assurance

Archivist:

Principal Investigator 1:

Quality Assurance at PI 1:

Principal Investigator 2:

Quality Assurance at PI 2:

1.3 Estimated Time Schedule

Study initiation date (Study plan final) [redacted]
Experimental starting date (Acclimatisation)
First application (day 1)
Necropsy (day 29)
Experimental completion date (histopathology results)
Study report (1st draft)
Study completion date (Study report final)

For organisational reasons, acclimatisation may start prior to finalisation of the study plan.

1.4 Test Guideline(s)

The procedures, principles, and objectives of this study plan abide the following guidelines:

- OECD Guideline for the Testing of Chemicals; Section 4: Health Effects: 407 Repeated Dose 28-day Oral Toxicity Study in Rodents (Updated Guideline, adopted 03th October 2008).

1.5 GLP-Compliance

[redacted] is a GLP- and GMP-certified test facility. A copy of the GLP certificate will be attached to the final report of this study. The Quality Assurance use in this study follows the principles of:

- Chemikaliengesetz (Chemicals Act) of the Federal Republic of Germany (ChemG) §19 and annexes 1 and 2 in the codified version of 02 July 2008 [BGBl. I S. 1146] amended in Federal Law Gazette, Germany (BGBL) from 02 November 2011, N. 56/2011, pp. 2162-2169.

[redacted]

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[redacted]

- 'OECD Principles of Good Laboratory Practice' (as revised in 1997) [ENV/MC/CHEM (98)17, January 21, 1998], and subsequent advisory/consensus OECD GLP documents 2-15 (where appropriate).

1.6 External Test Laboratories / Principal Investigator(s) (PI)

1.6.1 Hematology and serum biochemistry (PI 1)

The DIN EN ISO/IEC 17025:2005 certified external contract laboratory [redacted] in [redacted] will provide the blood chemistry data and the haemogram. The samples will be individually labelled at the time of exchange. [redacted] shuttle service will pick up the samples on the day of blood collection. Blood analysis will be performed 8 h after bleeding at maximum. Any surplus blood after analysis will be destroyed at the [redacted] test site. Data exchange takes place on standardised PC-printout-sheets, archived at the test facility with the raw data. As details regarding biological examinations are standardised by [redacted] and [redacted] SOP and are already summarised in this study plan, a separate phase plan issued by synlab is not required.

1.6.2 Histopathological examination

The preparation and fixation of the histological sections will be performed by [redacted] histology lab according to [redacted]

The analysis and interpretation of the sections will be conducted by [redacted] the external GLP test site [redacted] Data transfer and data recording will conform to [redacted] details regarding histopathological examinations are standardised and already summarised in this study plan, a separate phase plan issued by [redacted] is not required.

1.7 Archiving

The study data will be archived according to the principles of:

- OECD SERIES ON PRINCIPLES OF GOOD LABORATORY PRACTICE AND COMPLIANCE MONITORING, Number 15: Establishment and Control of Archives that Operate in Compliance with the Principles of GLP [ENV/JM/MONO(2007)10], (Advisory Document, effective 11-Jun-2007).

All raw data, documents, tissue samples, and other data of relevance retrieved or generated by [redacted] including the study plan, all applicable amendments, and the final

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[redacted]

report, will be stored in the archive for 15 years or however long is legally required. After that time period has elapsed, no data will be discarded without the Sponsor's notification.

Archiving of materials with storage requirements differing from conventional storage conditions may produce additional costs. Upon request of the Sponsor, archiving may be assigned to an adequate external GLP archive. Where retention samples of test items, reference items or other materials are taken, they will be stored for only as long as their substance quality allows for evaluation. The procedures for archiving are described by the internal Central archives paper/materials").

Storage throughout the study: The Study Director will be responsible for storing data in the proper lab-folder, protected from unauthorized access.

Storage after study completion: The A ll be responsible for storing data in the central GLP archive protected from unauthorized access.

1.8 Changes and Deviations to the Study Plan

Amendments (planned changes to the study plan) will be issued and signed by the Study Director and the QA at The Sponsor will receive the original amendment, which must be signed and returned to Amendments will become effective at the time of the Sponsor's signature. The Sponsor retains one copy. Amendments will be added to all copies of the study plan and distributed accordingly.

Deviations (unanticipated changes) to the study plan will be documented and signed by the Study Director and the QA and documented with the raw data. The study report will reflect any deviations. The Sponsor will be promptly informed of any relevant deviations from the study plan.

2 Test system

2.1 Test animals

Species	*Rattus norvegicus*
Strain	Wistar Han (IGS)
Gender	20 males, 20 females
Source	Charles River Sandhofer Weg 7 97633 Sulzfeld, Germany
Total number of animals	40
Age at acclimatisation	8-9 weeks
Health status	Specific pathogen free (SPF)
Pregnancy status females	Nulliparous, non-pregnant

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Acclimatisation	5-15 days

The purchase of animals as well as the identification, allocation and animal husbandry will be performed according to [redacted]

Rationale for chosen test species:

Wistar rats are commonly used and recommended to assess toxicity. A large number of publications and sufficient historic data of the test facility are available.

2.1.1 Animal husbandry

Room	OP 1
Housing conditions	Clean conventional housing: airing with approx. 10 air changes per hour, room climate 22 ± 3°C, relative humidity at 30-70%, (aimed limits - due to meteorological circumstances, actual relative humidity may be altered on short term), artificial lighting 12 h light/12 h dark
Caging	Groups of up to five animals of the same sex in open macrolon cages type 2000P, TechniPlast (size slightly larger than GV-SOLAS Type IV).
Bedding	Lignocel hygienic animal bedding (J. Rettenmaier & Söhne GmbH + Co. KG, 73494 Rosenberg)
Diet	Maintenance diet for rats and mice, No. 1324 TPF (Altromin Spezialfutter GmbH & Co. KG, 32791 Lage), *ad lib.*
Water	Sterilised community tap water, *ad lib.*

2.1.2 Allocation

Upon arrival at the test facility, the animals will be visually checked for signs of ill health and abnormalities. The animals will then be located in an animal facility room designated and documented in an according laboratory work sheet and will be acclimatised to the laboratory conditions for at least 5 days. All animals assigned to this study will be housed in the same room throughout the entire study time frame.

2.1.3 Stratification and randomisation

This study will be designed as a randomised controlled trial (RCT). Upon arrival at the test facility, rats will be weighed individually and grouped into three weight clusters per gender. The Study Director will decide whether rats delivered outside the defined body mass range will be excluded from the study.

[redacted]

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[redacted]

Single animals from the central clusters will be placed consecutively into prepared cages until the cluster is depleted. Animals from the remaining clusters will be caged alternately in the same manner.

Prepared cardboard labels containing the dose group will be riffled by hand by the TcO in charge and attached blindly onto the cages. The results of this pseudo-randomisation will be documented in the according laboratory work sheets.

Rationale for randomisation:

Concerning the avoidance of bias during the distribution of test animals, it is in accordance to current scientific knowledge that a pseudo-randomisation as described in chapter 2.1.3. will be sufficient to generate the modest amount of unpredictability required for preclinical and clinical studies.

2.1.4 Identification

Each animal in a cage will be identified by a single individual ear punch. Each cage will be labelled with a card displaying the cage number, the study number, information on the animals, and the respective dose group.

2.2 Test Item

The Sponsor will supply all data about the test item. Chemical analysis of the identity and the purity of the batch will not be part of this study. The Sponsor ensures that all test items, control items, substances or mixtures delivered to the test facility were appropriately tested for identity, strength, purity, stability and uniformity, according to guideline 21 CFR 58.31(d) where applicable.

Identification
Purity
CAS No.
Batch No.
Batch production
Appearance
Storage conditions
Expiry date
Solubility in water or ethanol
Stability
Hazard information

[redacted]

2.3 Vehicle

Identification Sterilised community tap water

[redacted]

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[redacted]

Supplier	Stadtwerke Gronau
Batch number	Not applicable
Purity	Not applicable
Storage conditions	Not applicable
Expiry date	Not applicable

2.3.1 Test item preparation

Identification	[redacted] suspended in sterilized tap water
Storage conditions	Prepared fresh daily
Stability	Unknown
Safety precautions	Wear suitable protective clothing, avoid dust formation, skin and eye contact

Instructions for test item preparation:

1. Determine gross vial mass of a screw top vial on an analytical balance
2. Add test item into screw top vial
3. Determine net mass of employed test item
4. Add required volume of water in order to produce the required application dose as stated in the laboratory work sheets
5. Vortex immediately before each dose will be drawn into the application syringe

The test item preparation is intended for an application volume of 5 ml per kg body weight. All material data sheets will be stored with the raw data.

[redacted]

[redacted]

3 Materials and Methods

3.1 General Study Design

The test item will be administered daily by oral gavage to 5 male and 5 female Wistar rats each at dose levels of 0, 111, 333 and 1000 mg/kg BW/day over a period of 28 days. Of these solutions, 5 ml/kg BW will be administered daily to each animal.

Test substances will be administered to rats of 8-9 week age at the start of the in-life phase. The first day of application is indicated as day 1.

During the in-life phase, viability, general and detailed clinical signs, food and water consumption, body weight, grip strength and reactivity to sensory stimuli will be monitored as scheduled in chapter 3.2.

At the end of the treatment period, blood samples from all animals will be drawn to provide data on haematology and serum biochemistry. Subsequently, all animals will be sacrificed and examined by gross necropsy. Tissues and organs will be preserved and processed for histopathological examination and organ mass will be recorded as specified in detail in table 3.

Group no.	Dose group	Number of animals (male/female)	Dose / BW [mg/kg]	Application volume / BW [ml/kg]
1	vehicle	5 / 5	0	5
2	low	5 / 5	111	5
3	medium	5 / 5	333	5
4	high	5 / 5	1000	5

Table 1: Dose groups

Rationale for the dose levels:

In a previously performed dose range finding study with dose escalation[1], the test item was administered in doses up to 1000 mg/kg body weight over a time period of 16 days and produced no observable toxic effects in the test animals. In accordance with the Sponsor, 1000 mg/kg was determined as high dose for this test.

3.2 Monitoring

The following parameters will be observed and documented during the in-life period:

- Viability/mortality — Twice daily
- General clinical signs/behaviour — Daily
- Detailed clinical signs (IRWIN-Test) — Once weekly (including once before beginning of application)
- Grip strength, Beam walking test — Once during the last exposure week

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[redacted]

- Body weight	Once weekly (including once before application start)
- Group food consumption	Once weekly (including once before application start)
- Group water consumption	Twice weekly (including once before application start)

3.2.1 Viability, general clinical signs and behaviour

Cage-side observations to detect signs of illness, reactions to treatment, moribundity, or mortality will be performed at least once daily throughout the study, up to the day of necropsy. Data will be recorded on checklists. In case of any findings, the individual animal will be examined by use of an extra „health status" form sheet.

3.2.2 Fatalities

In the case of a premature death of an animal during the in-life phase, the animal will be subjected to necropsy. On workdays, recently died animals will be dissected immediately after detection of the carcass. On non-workdays, animals found dead will be stored in a freezer at ≤ - 15°C and dissected on the next working day. After visual examination, the Study Director will decide on further tests, e.g. on recording organ weights, further preservation or an optional histopathological inspection.

3.2.3 Detailed clinical signs (IRWIN-test)

Individual monitoring of detailed clinical signs will be performed once before the first application, and once a week thereafter. Any findings will be noted on checklists, comprising

- changes in skin, fur, eyes, mucous membranes
- occurrence of secretions and excretions
- autonomic activity (e.g. lacrimation, piloerection, pupil size, unusual respiratory pattern)
- changes in gait, posture, and response to handling
- presence of clonic or tonic movements, stereotypies (e.g. excessive grooming, repetitive circling), bizarre behaviour (e.g. self-mutilation, walking backwards)
- and any other observed, unusual signs.

These procedures follow [redacted]

3.2.4 Grip strength and Beam walking test

In the last exposure week, additional recordings will be made of grip strength and reactivity to stimuli (beam walking test[1]).

For the grip strength analysis, rats gripping a small grid attached to a gauge will be pulled away from the grid. The maximum read-out of the balance shows the strength of the rat's grip on the grid.

[1] De Ryck *et al.* (1989), modified by Jolkkonen *et al.* (2000). [redacted]

[redacted]

For the beam walking test animals are placed on a small bar near a light source. The placing and the if so faults of placing the limbs on the bar will be documented and rated in a defined score system.

These procedures follow

3.2.5 Body weight, food and water consumption

Individual body weight, group food and group water consumption will be monitored as scheduled in chapter 3.2.

3.3 Terminal Procedures

3.3.1 Blood sampling, haematology, serum biochemistry and blood clotting time

On day 29, approx. 1100 µl blood will be taken from the retroorbital vein plexus of each animal immediately before sacrificing the animal. In order to avoid coagulation, 450 µl of each individual blood sample will be mixed with 50 µl 10x HEPES-EDTA solution directly after bleeding. 600 µl of the remaining blood will be filled in tw heparine syringes. One will be sent to the PI 1, the second will be used to prepare serum at These sera will be stored in a refrigerator at -20 +/-5 °C to allow a potential determination of thyroid hormones.

The EDTA-blood and one of the heparine blood samples per animal will be transferred to PI 1 to analyse parameters on haematology and serum biochemistry (see table 2) as well as blood clotting time. The samples will be individually labelled at the time of data exchange according to

o The shuttle service of the will pick up the samples on the day of blood collection. Blood analysis will be performed 8 h after bleeding at maximum. Any surplus blood after analysis will be disposed of at the test laboratory of PI 1.

The original results of the analysis will be returned to the hands of the study director at Data will be exchanged on standardised printout-sheets, archived at the test facility with the raw data.

Parameter	Unit
Leukocytes	x 10^3/µl
Erythrocytes	/pl
Reticulocytes	‰
Haemoglobin concentration (HB)	g/dl
Haematocrit (HKT)	%
Mean corpuscular volume (MCV)	fl
Mean corpuscular haemoglobin (MCH)	pg
Mean corpuscular haemoglobin conc. (MCHC)	g/dl
Platelets/thrombocytes	x 10^3/µl
Lymphocytes	%
Monocytes	%
Band neutrophil	%
Segmented neutrophil	%
Eosinophils	%
Basophils	%

Parameter	Unit
Sodium	mmol/l
Potassium	mmol/l
Chloride	mmol/l
Calcium	mmol/l
Glucose (in serum)	mg/dl
Total cholesterol	mg/dl
Urea	mg/dl
Creatinine	mg/dl
Total protein	g/dL
Albumin (in serum)	g/dL
Globulin	g/dL
A/G Ratio	n.a.
Alanine aminotransferase (ALT)[1]	U/l
Aspartate aminotransferase (AST)[2]	U/l
Alkaline phosphatase	U/l
Gamma glutamyl transferase (GGT)	U/l

[1]: designated in the raw data with its alternate name Glutamic-pyruvic transaminase (GPT)
[2]: designated in the raw data with its alternate name Glutamic-oxaloacetic transaminase (GOT)

Table 2: Haematological and serum biochemistry examinations

The in-life phase will be terminated on day 29. All animals will be sacrificed by asphyxiation in a CO_2 atmosphere. A full macroscopic examination will be performed. All possibly occurring lesions will be noted. Data will be recorded on checklists for each individual animal.

During necropsy of all animals, weights will be determined of the organs denoted by „W" in table 3; tissues denoted by „P" will be preserved in the appropriate fixative/s.

[redacted]

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[redacted]

Ref. No.	Tissue/organ	Procedure[1]
1	Gross lesions	P
2	Oesophagus	P
3	Trachea and thyroid	P
4	Stomach	P
5	Thymus	P, W
6	Liver	P, W
7	Spleen	P, W
8	Duodenum	P
9	Jejunum	P
10	Ileum (with Peyer's patches)	P
11	Cecum	P
12	Colon	P
13	Rectum	P
14	Lymph nodes (mesenterial)	P
15	Kidney	P, W
16	Vagina	P

Ref. No.	Tissue/organ	Procedure[1]
17	Adrenals	P, W
18	Urinary bladder	P
19	Testes/ovary	P, W
20	Epididymides	P, W
21	Prostata/uterus/cervix	P (W)
22	Heart	P, W
23	Lungs	P
24	Peripheral nerve	P
25	Bone marrow[2]	P
26	Sternum	P
27	Spinal cord	P
28	Whole brain	W
29	Cerebrum	P
30	Cerebellum	P
31	Pons	P
32	Eye	P
33	Skeletal muscle	P

[1]: P = preservation, W = weight determination
[2]: Bone marrow will only be examined if pathologic changes are observed in the sternum

Table 3: Necropsy, tissue preservation, and organ weights

3.4 Histology

Histological preparation of the organs and tissues denoted by „P" in table 3 will be performed from every animal of the high-dose and the vehicle group (see also chapter 1.6.2). The selected tissues will be preserved in the appropriate fixative/s embedded in paraffin wax, sectioned, and stained with hemalaum and eosin. The preparation and fixation of the raw materials for histological sectioning will be performed by [redacted] histology lab [redacted]

3.5 Histopathology

The stained sections will be transferred to the Principal Investigator 2 for histopathological examination. Data transfer and data recording will conform to [redacted] internal [redacted]

[redacted]

At animal heading data and necropsy findings recorded by during the postmortem examination will be taken from the postmortem records, translated into English and entered manually into an adequate computer system. The pathologist will document the findings during histopathological examination in an expert report. Therein, all observations will be presented for each individual rat in full descriptive terms. In addition, the incidence of histopathological findings will be presented in tabular form. Wherever possible, histological alterations will be described according to their distribution, severity, morphological characteristics and severity scores.

As details regarding histopathological examinations are standardised, a separate phase plan will not be necessary. The pathology expert report and the original histological slides will be returned to the hands of the Study Director. The results will be included in the study report. Histological materials will be archived for 15 years.

4 Content of Study Report

The Study Report will include but not be limited to the following information:

Identification of the study
- the descriptive title
- Identification of the test, reference and control items by name and code
- Identification of samples taken during the study by name and code.

Information concerning the sponsor and the test facility; name and address of
- the Sponsor
- the test facility
- the Study Director
- the responsible quality assurance person
- the archives responsible person
- the scientists having contributed to the final report.

Dates
- detailed experimental starting and completion dates of the several phases of the study.

Statements
- a GLP compliance statement authorized by the study director.
- a quality assurance statement listing the types of inspections made and their dates, including the phases inspected and the dates any inspection results were reported to the Study Director and test facility management. This statement will also serve to confirm that the final report reflects the raw data.

Description of materials and test methods
- detailed description of test methods and materials used (whenever possible in tabulated format).
- reference to relevant guidelines or other scientifically accepted descriptions of methods and procedures.

Results
- a summary of results (whenever possible in tabular format)
- all information and data required by the study plan
- a detailed presentation of the results (whenever possible in graphical format in the text and tabular format in the Appendix), including calculations and determinations of statistical significance
- an evaluation and discussion of the results and conclusions.

Archive
- the locations where the study plan, raw data and the final report have been archived.

The report will be submitted to the sponsor as draft for scientific review. A final report will be issued following receipt of the Sponsor's comments.

[redacted]

[redacted]

5 Distribution of Study Plan

[redacted]	Original
Study Monitor	One authorised copy
Principal Investigator 1	One authorised copy
Principal Investigator 2	One authorised copy

[redacted]

[redacted]

Appendix D: Certificates

[redacted]

Analysis profile of the test item

Short profile

Short profile

Commercial name:

Chemical Name:

CAS-Nummer:

CA-Index-Name:

Chemical formula:

Molecular weight:

Monomeric unit:

Appearance:

Purity:

Melting point:

Elemental analysis:

Impurities:

Solubility in water:

Short profile

Density:

Particle size:

Spectral data:

[redacted] Short profile [redacted]

NMR Spectra:

Due to the insolubility of the product it is not possible to measure spectra in solution. Hence solid state NMR spectra have been measured.

^{31}P NMR:

Instrument: BRUKER Avance-II 200 solid state-MAS Spectrometer with 4.7 T Magnet and Double resonance sample holder for 2.5mm rotors under magic angle spinning (MAS) conditions.

The frequency is given in ν_{MAS}. The chemical shifts are compared to the latest IUPAC recommendations for references [redacted]

[redacted]

[redacted]

Short profil

properties after unfolding:

HPLC:

The water solubility of the product is Further it is
Hence it is not possible to carry HPLC with this substance.

Synthesis:

Application:

Lab animal diet

14/12/2011 13:52 +495232608820 ALTROMIN GMBH S. 01

Nr.: QA - 72
Aufbewahrungsdauer:
10 Jahre nach Erstellen

Altromin Spezialfutter GmbH & Co. KG
Im Gestenkamp 20
D-32791 Lage
Tel.: +49 (0)5232 / 6088-0
Fax: +49 (0)5232 / 6088-50
E-Mail: analysen@altromin.de

Eingang 14.12.11
15.12.11

MAT 626

altromin

Analysen-Protokoll

Bezeichnung	Haltungsdiät für Ratten und Mäuse
Typ	1324 TPF
	verpackt à 5kg doppelt Vakuum
Kunde	Vivo Science GmbH, Gronau
Bezugenummer der Partie // Chargen-Nr.	220912//1230
Auftrags- / Bestellnr.	Altromin Beleg-Nr. 30682
Produktionsdatum	22.09.2011
Mindesthaltbarkeitsdatum	22.09.2012

Chemische Untersuchung

% in lufttrockener Substanz	Toleranzen*	
Rohprotein	17,1 – 21,85	19,3
Rohfett	3,2 – 5,2	4,5
Rohfaser	4,65 – 6,9	5,7
Rohasche	4,9 – 6,9	6,6
Feuchtigkeit	< 13,0	12,1
NfE		51,8

*Toleranzen gemäß „Leitlinien für die qualitätsgesicherte Herstellung von Versuchsfuttern" veröffentlicht (2001) von der Gesellschaft für Versuchstierkunde (GV-SOLAS)

Physikalische Untersuchung

Härtegrad kg/cm² - Kahl	20

Sensorische Untersuchung

Olfaktorischer Eindruck	ok
Visueller Eindruck	ok

Mikrobiologische Untersuchung

Aerobe Gesamtkeimzahl	< 10 KbE/g
Anaerobe Gesamtkeimzahl	< 10 KbE/g
Aerobe und anaerobe Sporenbildner	< 10 KbE/g

Kommentar

Auf der Grundlage o.g. Analysendaten entspricht die Diät den Qualitätsrichtlinien sowie den Spezifikationsvorgaben der Fa. Altromin und wurde daher zur Auslieferung freigegeben.

Datum: 03.11.2011

Hans-Leopold Altrogge
Qualitätskontrolle

Dieses Dokument wurde maschinell erstellt und ist daher ohne Unterschrift gültig.

[redacted]

stadtwerke gronau

Trinkwasseranalyse der Stadtwerke Gronau GmbH

gemäß TrinkwV 2001

Stand: April 2011

Bezeichnung	Einheit	Grenzwert gemäß TrinkwV 2001	Wasserwerk Gronau	Wasserwerk Epe
Mikrobiologische Parameter				
Clostridium perfingens	/100 ml	0	0	0
Coliforme Bakterien	/100 ml	0	0	0
Enterokokken	/100 ml	0	0	0
Escherichia coli (E. coli)	/100 ml	0	0	0
Koloniezahl bei 22 °C	/ml	100	0	0
Koloniezahl bei 36 °C	/ml	100	0	0
Chemische Parameter Teil I				
Benzol	mg/l	0,0001	< 0,0005	< 0,0005
Bor	mg/l	1	0,12	0,036
Bromat	mg/l	0,01	< 0,005	< 0,005
Chrom	mg/l	0,05	< 0,005	< 0,005
Cyanid	mg/l	0,05	< 0,005	< 0,005
1,2-Dichlorethan	mg/l	0,003	< 0,0005	< 0,0005
Fluorid	mg/l	1,5	0,15	0,11
Nitrat	mg/l	50	18	13
PBSM*	mg/l	0,0001	< 0,00005	< 0,00005
PBSM (insgesamt)	mg/l	0,0005	< 0,00005	< 0,00005
Quecksilber	mg/l	0,001	< 0,0002	< 0,0002
Selen	mg/l	0,01	< 0,005	< 0,005
Tetra-/Trichlorethen	mg/l	0,01	< 0,0005	< 0,0005
Chemische Parameter Teil II				
Antimon	mg/l	0,005	< 0,005	< 0,005
Arsen	mg/l	0,01	< 0,005	< 0,005
Benzo(a)pyren	mg/l	0,00001	< 0,000005	< 0,000005
Blei	mg/l	0,01	< 0,005	< 0,005
Cadmium	mg/l	0,005	< 0,0005	< 0,0005
Kupfer	mg/l	2	0,050	< 0,003
Nickel	mg/l	0,02	< 0,005	< 0,005
Nitrit	mg/l	0,5	< 0,01	< 0,01
PAK*	mg/l	0,0001	< 0,00002	< 0,00002
Trihalogenmethane*	mg/l	0,01	< 0,0005	< 0,0005
Indikatorparameter				
Aluminium	mg/l	0,2	< 0,022	0,031
Ammonium	mg/l	0,5	< 0,05	< 0,05
Chlorid	mg/l	250	33	40
Eisen	mg/l	0,2	< 0,011	< 0,018
Färbung (SAK 436 nm)	m^{-1}	0,5	0,3	0,4
Elektrische Leitfähigkeit	µS/cm	2500 bei 20 °C	559	613
Mangan	mg/l	0,05	< 0,005	0,037
Natrium	mg/l	200	26	21
Organisch gebundener Kohlenstoff (TOC)	mg/l	ohne anormale Veränderung	5,2	5,2
Sulfat	mg/l	240	64	66
Trübung	NTU	1	< 0,5	< 0,5
pH-Wert	–	6,5–9,5	7,6	7,4

stadtwerke gronau
fortschritt aus tradition

Bezeichnung	Einheit	Grenzwert gemäß TrinkwV 2001	Wasserwerk Gronau	Wasserwerk Epe
Allgemeine Parameter				
Temperatur	°C	–	10,6	9,8
Farbe	–	–	farblos	farblos
Geruch	–	–	geruchlos	geruchlos
Säurekapazität	mmol/l	–	4,0	4,9
Sauerstoffgehalt	mg/l	–	10,5	8,5
Calcium	mg/l	–	89	120
Kalium	mg/l	–	10,0	4,5
Magnesium	mg/l	–	7,8	5,6
Gesamthärte	°dH	–	14	18,0
Härtebereich	–	–	mittel	hart
Uran	µg/l	–	< 1	< 1
** in der Einzelsubstanz*				

Analysen: Trinkwasseranalysen vom 07.09.2010, 21.03.2011 und 26.04.2011 der Wessling Laboratorien GmbH Altenberge.

Das Trinkwasser der Stadtwerke Gronau GmbH wird nicht gechlort oder phosphatiert. Im Rahmen der Wasseraufbereitung verwenden wir Aluminiumsulfat, welches aber im Aufbereitungsprozess vollständig wieder entzogen wird.

Die Beschaffenheit des gelieferten Trinkwassers kann sich zeitweise in gewissen Grenzen ändern, z.B. durch Schwankungen in der Rohwasserqualität, durch vorübergehende Umstellungen in der Aufbereitung, durch Versorgung aus einem anderen Wasserwerk oder durch Reaktion in den Transportleitungen. Eine Haftung aufgrund der obigen Analysenangaben wird daher ausdrücklich ausgeschlossen.

Das Wasser der Stadtwerke Gronau kann ohne weitere Behandlung als Trinkwasser genutzt werden.

Wünschen Sie weitere Informationen zum Trinkwasser, stehen wir Ihnen gerne persönlich (Laubstiege 19, 48599 Gronau), telefonisch unter Ruf 02562 717-717 oder im Internet unter www.stadtwerke-gronau.de zur Verfügung.

Microbiological Analysis of the drinking water (November 2011)

WESSLING

WESSLING GmbH
Umweltanalytik
Oststraße 6 · 48341 Altenberge
Tel. +49 (0)2505 89-0 · Fax +49 (0)2505 89-119
www.wessling.de

WESSLING GmbH, Oststr. 8, 48341 Altenberge
[redacted]

Ansprechpartner: Nadine Averesch
Durchwahl: (02505) 89-152

E-Mail: Nadine.Averesch@wessling.de

Hygieneanalytik

Prüfbericht Nr. UAL11-18583-1 Auftrag Nr. UAL-02843-11 Datum 14.11.2011

Probe Nr.	11-126818-02
Eingangsdatum	08.11.2011
Bezeichnung	A 2
Probenart	Trinkwasser
Probenahme	07.11.2011
Probenahme durch	Auftraggeber
Probenmenge	1,5 Liter
Probengefäß	250 ml Schliffflasche 5x250 ml PE Kunststoffröhrchen
Anzahl Gefäße	7
Untersuchungsbeginn	08.11.2011
Untersuchungsende	14.11.2011

Anlage 1 - Teil 1 Mikrobiologische Parameter

Probe Nr.		Matrix			11-126818-02
Bezeichnung					A 2
			Min	Max	
Escherichia coli	KBE/100 ml	W/E		0 (GW)	0
Enterokokken	KBE/100 ml	W/E		0 (GW)	0

DAkkS Deutsche Akkreditierungsstelle D-PL-14162-01-00

Durch die DAkkS nach DIN EN ISO/IEC 17025 akkreditiertes Prüflaboratorium. Die Akkreditierung gilt für die mit A markierten Prüfverfahren. Messergebnisse beziehen sich ausschließlich auf die uns vorliegenden Prüfobjekte. Prüfberichte dürfen ohne Genehmigung der WESSLING Laboratorien nicht auszugsweise vervielfältigt werden.

Geschäftsführer: Hans-Dieter Bossemeyer, Dr. Micheela Nowak, Dr. Michael Preußer
HRB 1953 AG Steinfurt

[redacted]

WESSLING

WESSLING GmbH
Umweltanalytik
Oststraße 6 · 48341 Altenberge
Tel. +49 (0)2505 89-0 · Fax +49 (0)2505 89-119
www.wessling.de

Prüfbericht Nr. UAL11-18583-1 Auftrag Nr. UAL-02843-11 Datum 14.11.2011

Anlage 3 - Indikatorparameter

Probe Nr.		Matrix		11-126818-02
Bezeichnung				A 2
			Min Max	
Coliforme Keime	KBE/100 ml	W/E	0 (GW)	0
Chlorid (Cl)	mg/l	W/E	250 (GW)	36
Koloniezahl bei 22°C	KBE/ml	W/E		0
Koloniezahl bei 36°C	KBE/ml	W/E		1
Eisen (Fe)	mg/l	W/E	0,2 (GW)	0,063
TOC	mg/l	W/E		4,5
Sulfat (SO4)	mg/l	W/E	250 (GW)	62

Anlage 2 - Teil 2 Chemische Parameter

Probe Nr.		Matrix		11-126818-02
Bezeichnung				A 2
			Min Max	
Blei (Pb)	mg/l	W/E	0,025 (GW)	<0,005
Nickel (Ni)	mg/l	W/E	0,02 (GW)	<0,005
Zink (Zn)	mg/l	W/E		<0,01
Kupfer (Cu)	mg/l	W/E	2 (GW)	0,11
Nitrit (NO2)	mg/l	W/E	0,5 (GW)	<0,01

Sonstige mikrobiologische Untersuchungen

Probe Nr.		Matrix		11-126818-02
Bezeichnung				A 2
			Min Max	
Pseudomonas aeruginosa	KBE/100 ml	W/E		0
Endotoxine	I.E./ml	OS		2,5

Legende

RW: Richtwert, GW: Grenzwert, SW: Sollwert, SP: Spezifikationswert, MW: Maßnahmewert

Methode		Norm	ausführender Standort
Gereinigtes Wasser, Aqua purificata		Ph. Eur. 0008	Pharmaanalytik Münster
Escherichia coli und Coliforme Keime in Wasser		EN ISO 9308-1[A]	Produktanalytik Altenberge
Enterokokken in Wasser		EN ISO 7899-2, TrinkwV 2001[A]	Produktanalytik Altenberge
Koloniezahl 22/36°C in Wasser		EN ISO 6222 (K5)[A]	Produktanalytik Altenberge
Pseudomonas aeruginosa in Wasser		EN ISO 16266[A]	Produktanalytik Altenberge
Nitrit in Wasser/Eluat		EN 26777[A]	Umweltanalytik Altenberge
Chlorid in Wasser/Eluat		EN ISO 10304-1[A]	Umweltanalytik Altenberge
Sulfat in Wasser/Eluat		EN ISO 10304 D19/D20[A]	Umweltanalytik Altenberge
Metalle/Elemente in Wasser/Eluat (ICP-OES / ICP-MS)		ISO 17294-2	Umweltanalytik Altenberge
Gesamter organischer Kohlenstoff (TOC) in Wasser/Eluat		EN 1484 (H3)[A]	Umweltanalytik Altenberge
OS	Originalsubstanz		
W/E	Wasser/Eluat		

DAkkS Deutsche Akkreditierungsstelle D-PL-14182-01-00

Durch die DAkkS nach DIN EN ISO/IEC 17025 akkreditiertes Prüflaboratorium. Die Akkreditierung gilt für die mit [A] markierten Prüfverfahren. Messergebnisse beziehen sich ausschließlich auf die uns vorliegenden Prüfobjekte. Prüfberichte dürfen ohne Genehmigung der WESSLING Laboratorien nicht auszugsweise vervielfältigt werden.

Geschäftsführer: Hans-Dieter Bossemeyer, Dr. Michaela Nowak, Dr. Michael Preußer
HRB 1953 AG Steinfurt

[redacted]

WESSLING

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www.wessling.de

Prüfbericht Nr. UAL11-18583-1 Auftrag Nr. UAL-02843-11 Datum 14.11.2011

Beurteilung

Beim Vergleich der ermittelten Analysendaten mit den Grenzwerten der TrinkwV 2011 konnten keine Auffälligkeiten festgestellt werden.

Aus hygienisch-bakteriologischer Sicht entspricht die Wasserprobe den Anforderungen der TrinkwV 2011.

Dieses Dokument wurde elektronisch erstellt und ist auch ohne Unterschrift gültig.

Nadine Averesch
Dipl. Ing. Chemie; Kundenbetreuung

DAkkS Deutsche Akkreditierungsstelle D-PL-14162-01-00

Durch die DAkkS nach DIN EN ISO/IEC 17025 akkreditiertes Prüflaboratorium. Die Akkreditierung gilt für die mit A markierten Prüfverfahren. Messergebnisse beziehen sich ausschließlich auf die uns vorliegenden Prüfobjekte. Prüfberichte dürfen ohne Genehmigung der WESSLING Laboratorien nicht auszugsweise vervielfältigt werden.

Geschäftsführer: Hans-Dieter Bossemeyer, Dr. Michaela Nowak, Dr. Michael Preußer
HRB 1953 AG Steinfurt

[redacted]

GLP-certificate of TPC

Kopie
28.07.2008
28.07.2008

Ministerium für Landwirtschaft, Umwelt und Ländliche Räume des Landes Schleswig-Holstein [redacted]

Gute Laborpraxis / Good Laboratory Practice

GLP-Bescheinigung / Statement of GLP Compliance

(gemäß / according to § 19 b Abs. 1 Chemikaliengesetz)

Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 88/320/EG wurde durchgeführt am:

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 88/320/EEC at:

☐ Prüfeinrichtung / Test facility ☒ Prüfstandort / Test site

[redacted]

Prüfungen nach Kategorien / Areas of Expertise
(Gemäß / according ChemVwV-GLP Nr. 5.3 / OECD guidance)

(9) Histopathologische Untersuchungen von mikroskopischen Organpräparaten aus toxikologischen Prüfungen

Datum der Inspektion / Date of Inspection
(Tag.Monat.Jahr / day.month.year)

19. März 2008

Der genannte Prüfstandort befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.
Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass an diesem Prüfstandort die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

The above mentioned test site is included in the national GLP Compliance Programme and is inspected on a regular basis.
Based on the inspection report it can be confirmed, that this test site is able to conduct the aforementioned studies in compliance with the Principles of GLP.

MINISTERIUM FÜR LANDWIRTSCHAFT, UMWELT UND LÄNDLICHE RÄUME DES LANDES SCHLESWIG-HOLSTEIN 15

Unterschrift, Datum / Signature, Date

10.07.08

Dipl.-Biol. Katrin Lütjen, GLP-Kommission Schleswig-Holstein
(Name und Funktion der verantwortlichen Person / Name and function of responsible person)
Ministerium für Landwirtschaft, Umwelt, und Ländliche Räume des Landes Schleswig-Holstein, Mercatorstr. 3, 24106 Kiel
(Name und Adresse der GLP-Überwachungsbehörde/name and address of the GLP Monitoring Authority)

[redacted]

DAkkS
Deutsche
Akkreditierungsstelle

Deutsche Akkreditierungsstelle GmbH

Beliehene gemäß § 8 Absatz 1 AkkStelleG i.V.m. § 1 Absatz 1 AkkStelleGBV
Unterzeichnerin der Multilateralen Abkommen
von EA, ILAC und IAF zur gegenseitigen Anerkennung

Akkreditierung

Die Deutsche Akkreditierungsstelle GmbH bestätigt hiermit, dass das Prüflaboratorium

[redacted]

die Kompetenz nach DIN EN ISO/IEC 17025:2005 besitzt, Prüfungen im folgenden Bereich durchzuführen:

Bereich:	**Veterinärmedizinische Laboratoriumsdiagnostik**
Prüfgebiete:	Immunologie, Klinische Chemie, Mikrobiologie, Virologie
Prüfarten/-verfahren:	Ligandenassays, Mikroskopie, Photometrie, Partikeleigenschaftsbestimmungen mit automatisierten Verfahren, Kulturelle Untersuchungen, Agglutinationsteste, Elektrophorese, Elektrochemische Untersuchungen, Koagulometrie, Qualitative/semiquantitative Untersuchungsverfahren mit visueller Auswertung, Turbidimetrie, Titrimetrie, Refraktometrie, Infrarotspektroskopie
Prüfgegenstände:	Blut, Serum, Urin, Plasma, Punktat, Kot, Steine, Haut, Abstriche, Parasiten, Biopsiematerial, Gewebe, Katheterspitzen, Punktate, Gewebeflüssigkeiten, Sekrete, Tupferproben, Milch, Liquor, Sektionsmaterial, Haare, Schuppen, Hautgeschabsel,

Die Akkreditierungsurkunde gilt nur in Verbindung mit dem Bescheid vom 08.11.2010 mit der Akkreditierungsnummer D-PL-14016-01 und ist gültig bis 28.05.2014. Sie besteht aus diesem Deckblatt, der Rückseite des Deckblatts und der folgenden Anlage mit insgesamt 26 Seiten.
Registrierungsnummer der Urkunde: **D-PL-14016-01-00**

Frankfurt, 08.11.2010

i.V.
Uwe Zimmermann
Abteilungsleiter

Siehe Hinweise auf der Rückseite

[redacted]

GLP-certificate of [redacted] now [redacted]

Ministerium für Arbeit, Gesundheit und Soziales
des Landes Nordrhein-Westfalen

Fürstenwall 25, 40219 Düsseldorf

Aktenzeichen II A 5 – 31.11.38.02

Gute Laborpraxis/Good Laboratory Practice
GLP-Bescheinigung/Statement of GLP Compliance
(gemäß/according to § 19b Abs. 1 Chemikaliengesetz)

Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 88/320/EG wurde durchgeführt in:

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 88/320/EEC at:

☒ Prüfeinrichtung/Test facility ☐ Prüfstandort/Test site

[redacted]

Prüfungen nach Kategorien	Areas of Expertise
Kategorie 2	category 2
Prüfungen zur Bestimmung der toxikologischen Eigenschaften	toxicity studies
Kategorie 9	category 9
Immuntoxikologie und Immunogenität in vitro und in vivo	Immunotoxicology and Immunogenicity in vitro and in vivo

Datum der Inspektion
23. bis 24. April 2008

Date of Inspection
on 23 until 24 April 2008

Die genannte Prüfeinrichtung befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

The above mentioned test facility is included in the national GLP Compliance Programme and is inspected on a regular basis.

Based on the inspection report it can be confirmed, that this test facility is able to conduct the aforementioned studies in compliance with the Principles of GLP.

Düsseldorf, den 24. Juli 2008
Im Auftrag

(Dr. Helmut Deden)

Land Nordrhein-Westfalen 13 Ministerium für Arbeit, Gesundheit und Soziales

Dienstsiegel/official-seal

[redacted]

EINGEGANGEN
19. Jan. 2009

Ministerium für Arbeit,
Gesundheit und Soziales
des Landes Nordrhein-Westfalen

Ministerium für Arbeit, Gesundheit und Soziales Nordrhein-Westfalen, 40190 Düsseldorf
[redacted]

Datum: 14 Januar 2009
Seite 1 von 1

Aktenzeichen II A 5 31.11
bei Antwort bitte angeben

Herr Wille
Telefon 0211 855-3535
Telefax 0211 855-3705
juergen.wille@mags.nrw.de

Namensänderung

Ihr Schreiben vom 06.01.2009

Sehr geehrte Damen und Herren,

vom 23.04.08 bis 24.04.08 wurde in der [redacted] eine Inspektion über die Einhaltung der Grundsätze der Guten Laborpraxis nach Anhang 1 des Chemikaliengesetzes (ChemG in der Fassung der Bekanntmachung vom 2. Juli 2008 (BGBl. I S.1146)) von einem Inspektorenteam aus Nordrhein-Westfalen durchgeführt. Wie Sie mit o.g. Schreiben mitteilten, hat sich der Name Ihrer Firma [redacted] geändert. Die Arbeitsgebiete und die Organisationsstruktur der GLP-Prüfeinrichtung sind von dieser Änderung nicht betroffen. Das GLP-Zertifikat vom 24.08.2008 behält somit weiterhin seine Gültigkeit.

Mit freundlichen Grüßen
Im Auftrag

Andrea Mayer-Figge
(Dr. Andrea Mayer-Figge)

Dienstgebäude und Lieferanschrift:
Fürstenwall 25,
40219 Düsseldorf
Telefon 0211 855-5
Telefax 0211 855-3683
poststelle@mags.nrw.de
www.mags.nrw.de

Öffentliche Verkehrsmittel:
Rheinbahn Linien 704, 709
Haltestelle: Stadttor
Rheinbahn Linien 719, 725
Haltestelle: Polizeipräsidium

Confirmation of the monitoring authority that the GLP certificate issued to the predecessor company [redacted] stays legally valid for [redacted]

[redacted]