

CORNING Hazleton

The HSD Sprague Dawley SD Rat - No more fat rat blues!

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Introduction
Regulatory guidelines for the investigation of the carcinogenic potential of a compound require animals to be treated for 2 years and ideally survival in each group to be approximately 50% on completion of this period. Over recent years it has been noted that the survival of the Charles River Sprague Dawley (Cr:CDBR) rat routinely used at this and other laboratories is diminishing, with the onset of tumours occurring in younger rats. The reasons behind the shortened life span and early tumour onset have been considered to be related to the high food consumption and obesity of Cr:CDBR animals. To overcome the problem of obesity, and therefore survival, in Cr:CDBR rats different approaches are available e.g. caloric restriction, increased group size, use of a different strain not prone to obesity e.g. Wistar. As the greater part of the data produced in toxicological studies is obtained from Sprague Dawley rats, an alternative source of the strain, which has been subjected to different derivation to the Cr:CDBR could also be considered. As part of a continuing program of background investigations, a study was established at the Corning Hazleton laboratories in Harrogate to investigate the background tumour incidence and toxicology data for the Harlan Sprague Dawley (HSD) rat. A comparison with the Cr:CDBR rat is ongoing with a view to offering an alternative strain to our clients.

Methods
One hundred and thirty rats of each sex were obtained from Harlan Olac Ltd in April 1994. Groups of twenty animals of each sex were sacrificed at 4, 13, 26 and 52 weeks, the remaining animals (150 of each sex) being maintained for 104 weeks. Animals were housed in groups of five/cage and had *ad libitum* access to food. Body weight and food consumption were measured at regular intervals along with full haematology, clinical chemistry, urine and ophthalmological screens up to Week 52. At each sacrifice, organ weights and macroscopic and microscopic examination of all tissues required by major regulatory authorities were performed. In addition to these investigations, swimming maze tests were performed. Littering and littering performance of the Harlan Sprague Dawley rat were evaluated in a separate reproduction toxicity study performed concurrently and using males from this study.

Results
Recent data from control Cr:CDBR animals at this laboratory have been included to provide the data presented for these animals.

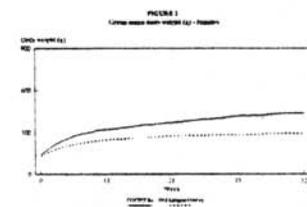
Body weight
The group mean body weight of the HSD and Cr:CDBR rats are compared at key intervals.

Study Duration	HSD		Cr:CDBR		HSD as a % of Cr:CDBR	
	Male	Female	Male	Female	Male	Female
4	285	191	390	240	66	80
13	392	245	550	315	71	78
26	459	273	670	265	69	75
52	506	294	760	440	67	67

The body weight of the male HSD rat is consistently 60-70% lower than the Cr:CDBR rat of a comparable age. Among females, while the body weight is lower in the earlier weeks, the differences between the two animal groups becomes more pronounced as the animals age.

nounced as the animals become older.

Food consumption
The group mean food consumption of the HSD and Cr:CDBR rats are compared at key intervals.



Graph 1: Food consumption - Females

Study Duration	HSD		Cr:CDBR		HSD as a % of Cr:CDBR	
	Male	Female	Male	Female	Male	Female
4	154	127	220	145	70	88
13	153	118	195	140	78	84
26	147	111	200	150	75	74
52	152	115	195	150	78	77

The amount of food consumed is consistently lower in the HSD animals than in Cr:CDBR animals. As with body weight, the differences between the female groups becomes more pronounced as the animals age.

Clinical pathology

A complete range of clinical pathology parameters routinely requested by regulatory authorities were measured at 4, 13, 26 and 52 weeks. The data was very consistent within the HSD group and was broadly comparable to the values obtained for Cr:CDBR rats.



Figure 3: Isophilic tubules in the kidney of a male HSD rat aged approximately 30 weeks

Pathology

The findings in the HSD strain of rat were generally very minor and of a similar nature and severity to those in Cr:CDBR rats of a similar age kept under our conditions. In addition a very minor glomerulonephropathy was noted in HSD rats at the 26 and 52 week kills.

Tumour incidence

At 52 weeks the incidence of masses (expressed as a percentage of animals showing masses/number of animals on study) were as follows:

Type of Mass	HSD		Cr:CDBR	
	Male	Female	Male	Female
Small moveable masses	8.67	6.67	1.67	23.33
Large moveable masses	0.07	5.33	0	5.00
Small stationary masses	22	31.33	0	5.00
Large stationary masses	0.07	1.33	0	1.67

It is noted that there appears to be a high incidence of small stationary masses among HSD rats. These masses are generally confined to the ventral hind region and have been apparent at palpation for many weeks. On examination they are considered likely to be enlarged preputial/clitoral glands or prominent lymph nodes. The main reason why these masses are so prevalent among HSD animals is probably due to their thinner nature. Enlarged glands do occur in the Cr:CDBR rats but due to the excess weight of these animals the masses are difficult to palpate.

There is no apparent difference in the occurrence of large masses in the two groups at Week 52.

Survival

The number of deaths (expressed as a percentage of the total number of animals starting study) at selected time intervals are as follows:

Study duration	HSD		Cr:CDBR	
	Male	Female	Male	Female
4	0	0	0	0
13	0	0	1.5	1.5
26	0	0	1.5	3
52	2.0	2.7	4.6	10

Conclusion

Data obtained to date on the Harlan Sprague Dawley show this rat to be a much lower body weight throughout its life span and lower food consumption than the Cr:CDBR rat. There is no indication from the pathology of the incidence of masses or survival to date of any unusually high incidence of findings which would preclude the use of this animal on toxicological studies of any duration.

These findings are in agreement with other data published on the HSD rat [1, 2]. The current indications suggest the strain is suitable for assessing the carcinogenic potential of compounds and a good alternative to the Charles River rat if the strain of choice is the Sprague Dawley.



Figure 1: Female HSD rat

[1]: Body weight and survival of Harlan vs. Charles River Sprague Dawley rats: implications for carcinogenicity testing. Matray-Devoti J, Sharp FF, Davies MH, Sorber MB, Schwabenbauer C [2]: A comparison study of the Cr:CDBR (CD) and Hsd:Sprague Dawley SD rat. Pettersen JC, Saunco DR, Pavkov KL, Matheson DW, Schwartz DR

Key Words:

Harlan Sprague Dawley rat, general toxicology, longevity, carcinogenicity



Figure 2: Male HSD rat

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Background 104 Week Study in the Harlan SD Rat

HUK Study: 0000/119

Study Director: Janet Kelly

Week 104

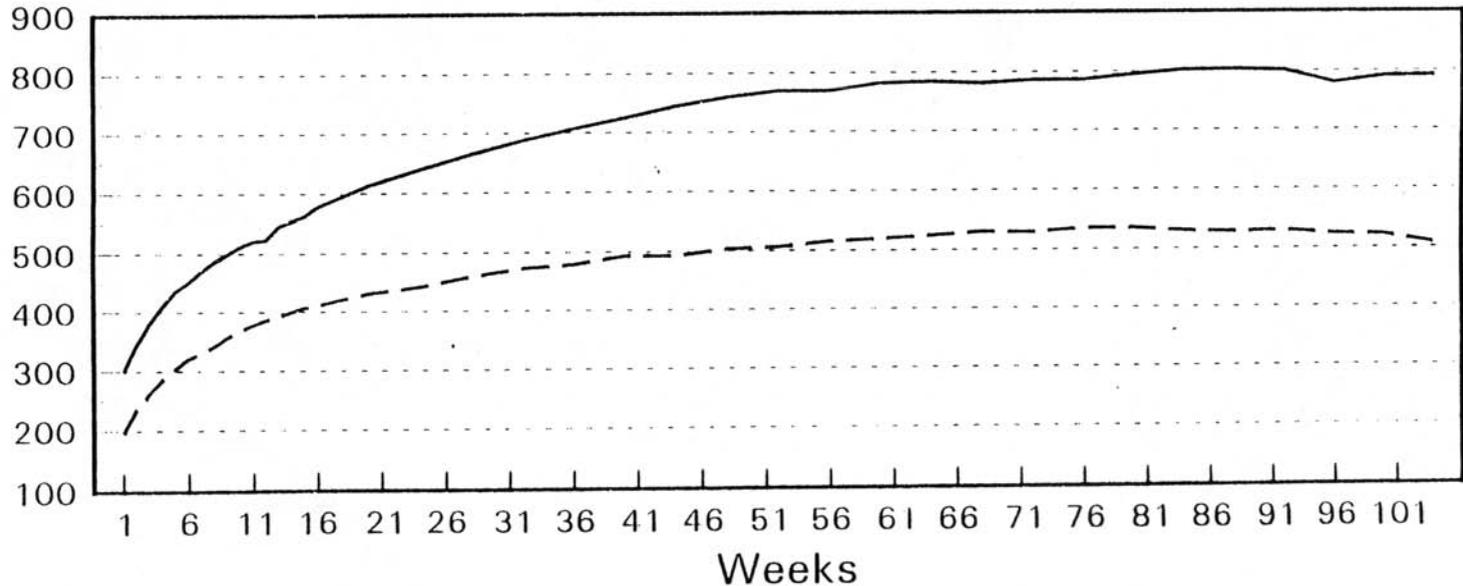
Group	Group size	Week of termination	Survival at termination	Body weight Week 13 (g)	Body weight Week 24* (g)	Body weight Week 52 (g)	Body weight Week 104 (g)	Food consumption at termination g/rat/week
1M	20	4	100	-	-	-	-	157
2M	20	13	100	383	-	-	-	150
3M	20	26	100	377	432	-	-	145
4M	20	52	100	382	453	499	-	151
5M	150	104	65	392	469	507	509	136
1F	20	4	100	-	-	-	-	116
2F	20	13	100	150	-	-	-	119
3F	20	26	100	145	270	-	-	105
4F	20	52	100	143	277	297	-	114
5F	150	104	49	153	273	294	329	134

Comments: * - last body weight before Week 26

CR vs HSD comparison

Male Growth

Grams



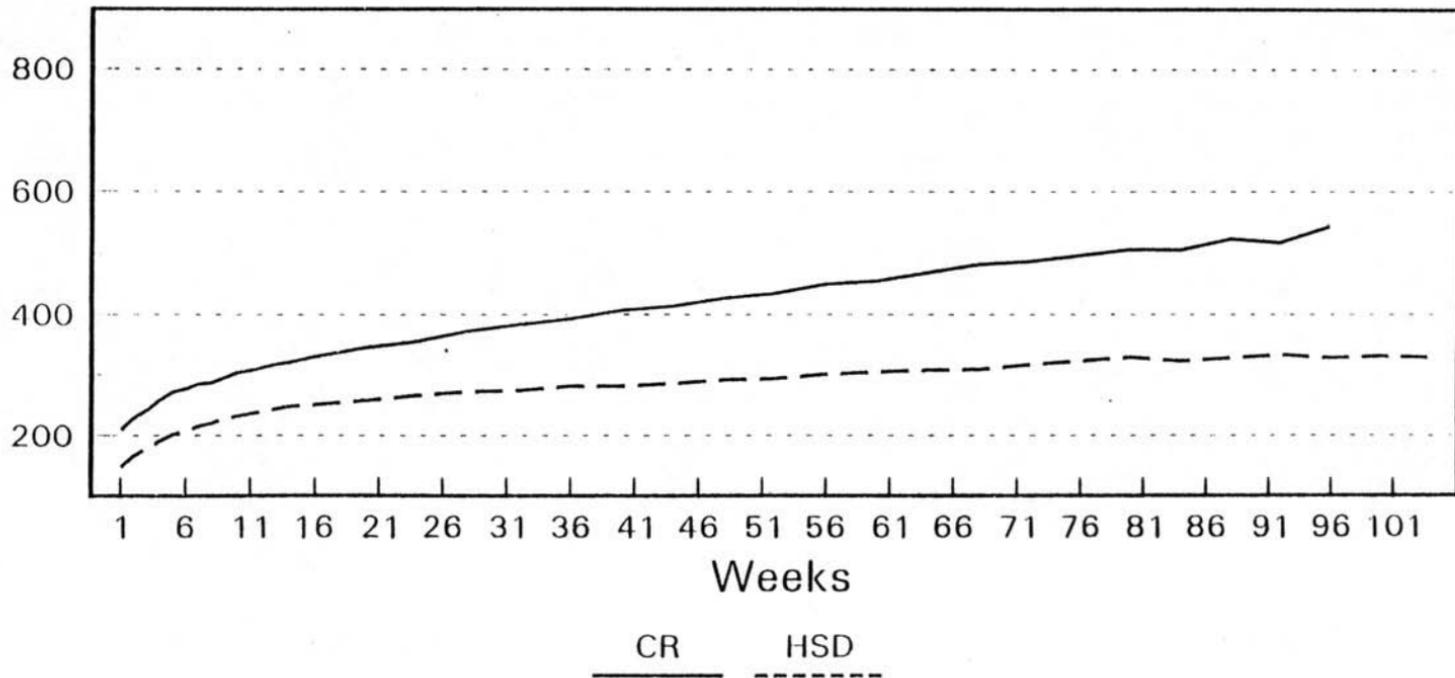
CR

HSD

CR vs HSD comparison

Female Growth

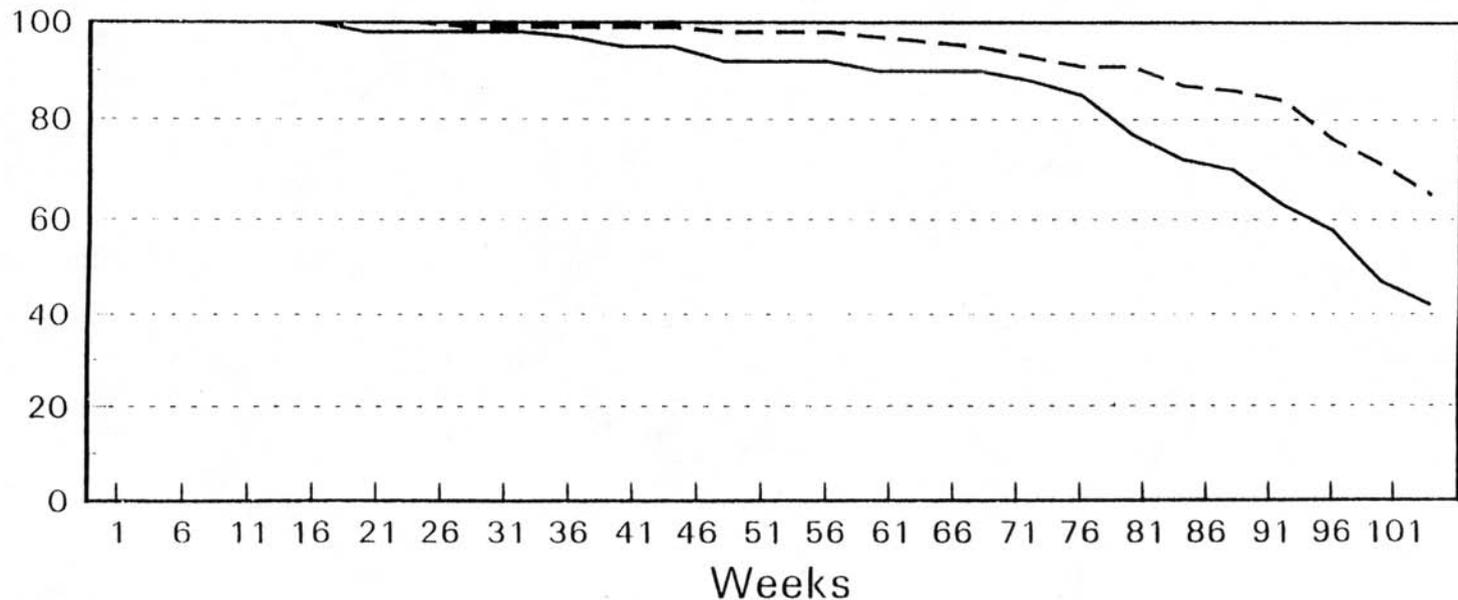
Grams



CR vs HSD comparison

Survival-Males

% alive



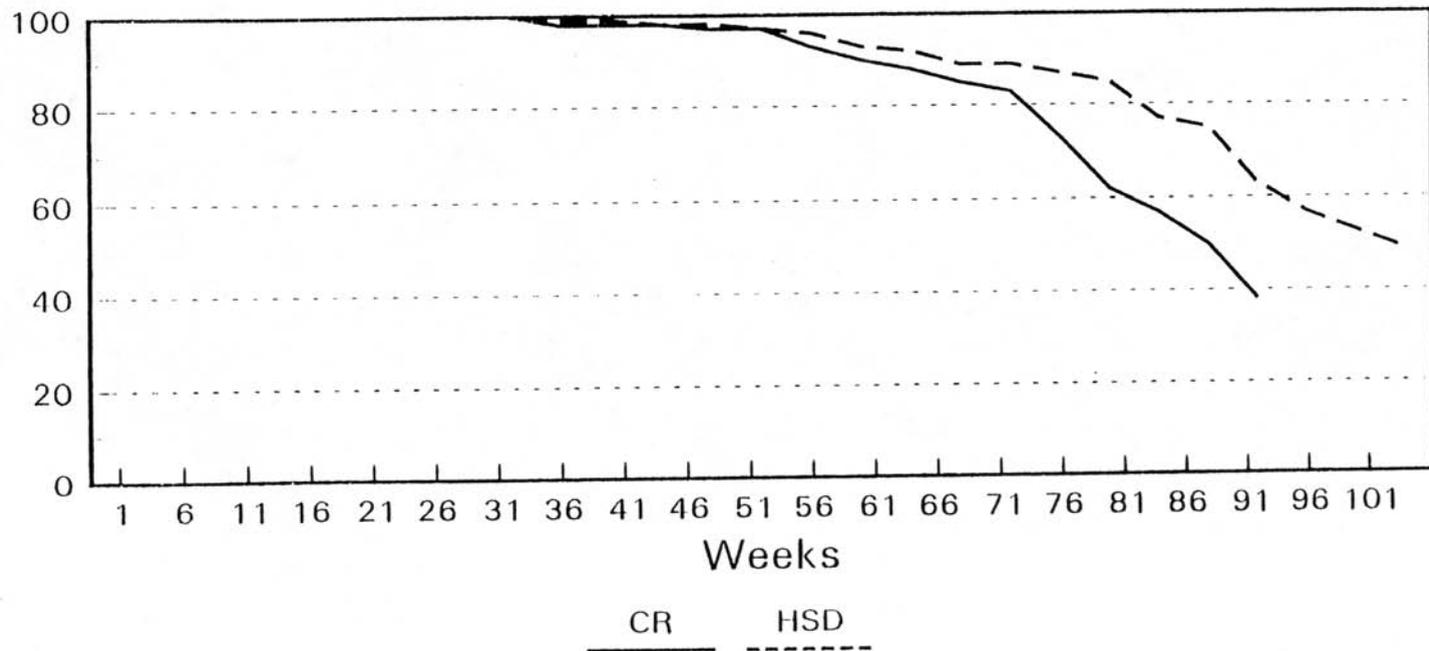
CR

HSD

CR vs HSD comparison

Survival-Females

% alive



CR vs HSD COMPARISONSUMMARY OF MACROSCOPIC LESIONS

SEX	HSD		CR	
	MALE	FEMALE	MALE	FEMALE
NO EXAMINED	98/150	74/150	25/60	20/60
<u>SKIN & SUBCUTIS</u>				
MASS 1	77%	76%	68%	70%
MASS 2	31%	43%	32%	40%
MASS 3		23%	16%	5%
TOTAL MASSES	36%	151%	124%	130%
<u>KIDNEY</u>				
IRREGULAR SURFACE	51%	11%	8%	
CYST	10%		4%	
<u>LIVER</u>				
MOTTLED	9%	3%	32%	35%
<u>ADRENAL</u>				
LARGE	13%	3%	16%	20%
DARK AREA	13%	3%	4%	5%
<u>STOMACH</u>				
THICK	34%	14%	0%	5%
<u>PITUITARY</u>				
MASS	1%	16%	0%	50%
<u>OVARY</u>				
CYST	0%	23%	0%	25%
<u>UTERUS</u>				
DISTENSION	0%	20%	0%	28%
<u>LUNG</u>				
PALE AREA	7%	27%	4%	0%

GROUP INCIDENCE: HISTOPATHOLOGY - ALL DATA

Kill type: All

Tissue	Group:	1	2	3	4	1	2	3	4
	Sex:	M	M	M	M	F	F	F	F
Observation	Number:	20	20	20	20	20	20	20	20
Heart									
Number examined		20	20	19	18	20	20	20	20
Inflammatory cell foci		2	2	1	3	1	0	0	1
Myocarditis/fibrosis		0	0	1	5	0	0	0	0
Ileum									
Number examined		20	20	19	18	20	20	20	20
Parasite		0	0	1	0	0	0	0	0
Jejunum									
Number examined		20	20	19	18	20	20	20	20
Distension		0	0	0	1	0	0	0	0
Kidney									
Number examined		20	20	20	20	20	20	20	20
Cyst		0	0	0	0	0	0	0	1
Tubular dilatation		0	1	0	0	0	0	0	0
Basophilic tubules		5	5	0	0	4	4	0	0
Focal nephropathy		5	13	1	0	2	2	3	2
Glomerulonephropathy		0	0	15	19	0	0	10	16
Hyaline droplets		1	1	0	0	0	0	0	0
Casts		1	0	0	0	0	0	0	0
Cortical mineralisation		0	0	0	0	0	0	1	2
Corticomedullary mineralisation		0	0	0	0	0	0	0	1
Papillary mineralisation		0	2	0	6	0	4	4	3
Pelvic mineralisation		0	0	0	2	0	0	1	8
Inflammatory cell foci		0	0	1	0	0	6	0	1
Capsular fibrosis/acnesion		0	0	0	0	0	0	1	0
Pyelitis		0	0	0	0	0	1	0	0
Lacrimal gland									
Number examined		20	20	20	20	20	20	20	20
Inflammatory cell foci		0	0	0	4	0	0	0	1
Adenitis		1	0	0	4	1	0	0	0
Harderian gland alteration		13	19	16	19	0	13	9	15
Liver									
Number examined		20	20	20	20	20	20	20	20
Caudate lobe necrosis		0	1	0	0	0	0	0	0
Inflammatory cell foci		19	18	18	20	16	19	20	20
Biliary proliferation		0	0	0	1	0	0	0	0
Vacuolated focus		0	0	0	1	0	0	0	0
Eosinophilic focus		0	0	0	2	0	0	0	0
Lung									
Number examined		20	20	20	20	20	20	20	20
Ectopic bone		1	1	3	1	1	0	1	0
Inflammatory cell foci		2	17	2	13	5	13	2	5
Foamy histiocytes		0	3	3	14	0	5	8	15
Pneumonitis		10	2	4	9	7	2	3	6

GROUP INCIDENCE: HISTOPATHOLOGY - ALL DATA

Kill type: All

	Group:	1	2	3	4	1	2	3	4
Tissue	Sex:	M	M	M	M	F	F	F	F
Observation	Number:	20	20	20	20	20	20	20	20
Mammary gland (female)									
Number examined		-	-	-	-	20	20	20	20
Cystic hyperplasia		-	-	-	-	0	0	0	1
Mandibular lymph node									
Number examined		20	20	19	18	20	20	20	20
Agonal congestion/haemorrhage		1	2	0	4	1	1	2	5
Lymphoid hyperplasia		2	4	1	1	1	1	3	2
Muscle									
Number examined		20	20	20	18	20	20	20	20
Inflammatory cell foci		0	0	1	0	0	0	0	0
Myositis		0	0	1	0	0	0	0	0
Oral cavity									
Number examined		0	0	0	0	0	0	1	0
ODONTOGENIC TUMOUR		0	0	0	0	0	0	1	0
Optic nerve									
Number examined		20	20	17	18	20	20	20	20
Neuropathy		0	3	0	2	7	2	4	5
Ovary									
Number examined		-	-	-	-	20	20	20	20
Oestrous cycle		-	-	-	-	0	0	1	1
Cyst		-	-	-	-	0	1	1	1
Reduced corpora lutea		-	-	-	-	0	0	4	12
Pancreas									
Number examined		20	20	19	19	20	20	20	20
Lobular atrophy		0	0	0	2	0	0	1	0
Pancreatitis		0	1	0	0	0	0	1	0
Basophilic focus		0	0	0	1	0	0	0	0
Preputial gland									
Number examined		0	0	2	3	-	-	-	-
Cystic distension		0	0	1	0	-	-	-	-
Adenitis		0	0	0	1	-	-	-	-
Abscess		0	0	1	2	-	-	-	-
Pituitary									
Number examined		20	20	19	19	20	20	20	20
Cyst		0	0	0	1	0	0	0	0
Cystic cleft		0	0	0	1	0	0	0	0
Prostate									
Number examined		20	20	19	18	-	-	-	-
Inflammatory cell foci		0	1	0	0	-	-	-	-

GROUP INCIDENCE: HISTOPATHOLOGY - ALL DATA

Kill type: All

Tissue	Group:	1	2	3	4	1	2	3	4
Observation	Sex:	M	M	M	M	F	F	F	F
	Number:	20	20	20	20	20	20	20	20
Rectum									
Number examined		20	20	18	19	20	20	20	20
Parasite		0	1	2	4	0	3	1	3
Salivary gland									
Number examined		20	20	19	19	20	20	20	20
Inflammatory cell foci		0	1	0	1	0	0	0	0
Adenitis		0	1	0	2	0	0	0	0
Skin - subcutis									
Number examined		20	20	19	19	20	20	20	20
Myositis		0	0	0	1	0	0	0	0
Dermatitis/folliculitis		0	0	1	1	0	0	0	0
Spleen									
Number examined		20	20	19	18	20	20	20	20
Barbiturate lysis		0	0	0	0	0	0	2	0
Pigment		0	0	1	13	0	0	14	15
Haemopoiesis		0	0	0	0	0	0	0	1
Capsular fibrosis		0	0	1	0	0	0	0	0
Stomach									
Number examined		20	20	19	19	20	20	19	20
Squamous cyst		0	0	0	0	0	0	1	0
Cystic glands		1	1	1	12	1	0	0	5
Gastritis		1	2	1	2	0	0	0	0
Forestomach gastritis		1	1	0	0	1	0	0	0
Erosion/ulcer		0	0	0	1	0	0	0	0
Seminal vesicle									
Number examined		20	20	19	18	-	-	-	-
Contraction		0	0	0	2	-	-	-	-
Tail									
Number examined		1	1	2	11	0	0	3	3
Necrosis		0	0	0	1	0	0	0	0
Dermatitis/folliculitis		1	1	2	11	0	0	3	3
Testis									
Number examined		20	20	19	19	-	-	-	-
Atrophy		0	0	1	3	-	-	-	-
Haemorrhage		0	1	0	0	-	-	-	-
Thymus									
Number examined		20	20	19	18	20	20	20	20
Ectopic thyroid		0	0	0	0	1	0	0	1
Cyst		0	0	0	0	0	2	7	11
Atrophy		0	0	0	1	0	0	0	1
Agonal congestion/haemorrhage		5	2	0	1	4	3	0	0
Lymphoid hyperplasia		0	1	0	0	0	0	0	0

GROUP INCIDENCE: HISTOPATHOLOGY - ALL DATA

Kill type: All

Tissue	Group:	1	2	3	4	1	2	3	4
	Sex:	M	M	M	M	F	F	F	F
Observation	Number:	20	20	20	20	20	20	20	20
Tongue									
Number examined		20	20	19	18	20	20	20	20
Glossitis		0	0	1	0	0	0	0	0
Thyroid									
Number examined		20	20	19	20	20	20	20	20
Cystic follicles		0	0	0	1	0	0	0	1
Inflammatory cell foci		0	0	0	1	0	0	0	0
Follicular cystic hyperplasia		0	0	0	0	0	0	0	1
C-cell hyperplasia		0	0	1	14	0	0	0	3
Urinary bladder									
Number examined		20	20	19	18	20	20	20	20
Cystitis		0	0	0	0	0	1	0	0
Uterus									
Number examined		-	-	-	-	20	20	20	20
Oestrous cycle		-	-	-	-	2	3	2	3
Cyst		-	-	-	-	1	0	0	4
Cystic glands		-	-	-	-	0	1	3	12
Agonal congestion/haemorrhage		-	-	-	-	0	0	0	2
Squamous metaplasia		-	-	-	-	0	0	3	0
DECIDUOMA		-	-	-	-	0	1	0	0
Vagina									
Number examined		-	-	-	-	20	20	20	20
Mucification		-	-	-	-	0	0	1	0
Zyomal gland									
Number examined		18	19	18	17	17	16	19	17
Cyst		0	0	0	1	0	0	0	0