

Tab. C.5.a.7.

PATHOLOGY REPORT	PAGE : 781
STATISTICAL EVALUATION	BOE PROJECT: G 70
TEST ARTICLE : SMD 919 CL 2 Y	PATHOL. NO.: 91009 HEW
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING	DATE : 11-MAY-93
SPONSOR : BOEHRINGER INGELHEIM KG	PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
COMBINED PREVALENCE AND DEATH RATE METHOD (PETO ET AL., 1980)

DOSE GROUPS : G0, G1, G2, G3, G4
SEX: MALE
STATUS AT NECROPSY: KO INCL. +
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
BRAIN	OLIGODENDROGLIOMA	2.204-	0.2776
LUNGS	ADENOMA	5.941+	0.4052#
LUNGS	CARCINOMA	2.197-	0.2776
TONGUE	CARCINOMA/SQUAMOUS	2.128-	0.2810
LIVER	ADENOMA/HEPATOC.	13.911-	0.1611#
LIVER	HEMANGIOSARCOMA	11.670-	0.1660#
LIVER	CARCINOMA/HEPATOC.	2.172-	0.3409
TESTES	LEYDIG CELL TUMOR	18.343+	0.0901#
PROSTATE	ADENOMA	2.203-	0.2776
SEMINAL VESICLES	LEIOMYOMA	2.176-	0.2776
PITUITARY GLAND	ADENOMA/P. DISTALIS	2.553-	0.2611
THYROID (BOTH LOBES)	CARCINOMA/FOLLICULAR	0.190-	0.4797
ADRENAL CORTEX	ADENOMA/B-CELL	2.901-	0.4286#
ADRENAL CORTEX	ADENOMA/Z. FASCICUL.	8.888-	0.1151#
ADRENAL CORTEX	ADENOMA/B-CELL/EXTD.	35.780-	0.0094#
ADRENAL CORTEX	ADENOMA/A-CELL	1.876-	0.3050
ADRENAL MEDULLA	MEDULL. TUMOR/BENIGN	2.190-	0.2776
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	6.288-	0.1635
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	1.540+	0.4626#
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	7.369+	0.3228#
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	7.470-	0.2539
SYSTEMIC NEOPLASMS	MAST CELL TUMOR	2.517-	0.3483
SPLEEN	HEMANGIOSARCOMA	0.176-	0.4813
HARDERIAN GLANDS	ADENOMA	12.472-	0.0808
SKIN	HEMANGIOSARCOMA	2.405-	0.2611
SKIN	LIPOMA	2.149-	0.2776
BODY CAVITIES	SARCOMA/OSSIFYING	5.671+	0.1379

-?? highest con. #10

-highest in con.

Explanation of Symbols

- p = one-tailed p-value
- = negative trend
- + = positive trend
- # = number of animals with tumors > 5% in at least one sex/dose group

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PATHOLOGY REPORT
STATISTICAL EVALUATION

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TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR : BOEHRINGER INGELHEIM KG

PATHOL. NO.: 91009 HEW
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
COMBINED PREVALENCE AND DEATH RATE METHOD (PETO ET AL., 1980)

DOSE GROUPS : G0,G1,G2,G3,G4
STATUS AT NECROPSY: K0 INCL. +
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

SEX: MALE

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
BODY CAVITIES	LIPOMA	0.000+	0.5000#

POOLED ORGANS/FINDINGS

SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA		
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA		
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	0.736+	0.4876#

POOLED ORGANS/FINDINGS

ADRENAL CORTEX	ADENOMA/B-CELL		
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.		
ADRENAL CORTEX	ADENOMA/B-CELL/EXTD.		
ADRENAL CORTEX	ADENOMA/A-CELL	45.819-	0.0158#

DOSE GROUPS : G0,G1,G2,G3,G4
STATUS AT NECROPSY: K0 INCL. +
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

SEX: FEMALE

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
BRAIN	NEOPLASM (NOS)	7.706+	0.0192
LUNGS	ADENOMA	19.597-	0.1788#

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 PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
 COMBINED PREVALENCE AND DEATH RATE METHOD (PEYO ET AL., 1980)

DOSE GROUPS : G0, G1, G2, G3, G4
 STATUS AT NECROPSY: K0 INCL. +
 TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

SEX: FEMALE

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
LUNGS	CARCINOMA	9.616-	0.1170
LIVER	ADENOMA/HEPATOC.	2.242-	0.2743
LIVER	HEMANGIOSARCOMA	4.326-	0.1977
URINARY BLADDER	CARCINOMA/TRANSIT.C.	7.731+	0.0192
OVARIES	ADENOMA/TUBULAR	8.839-	0.1587
OVARIES	TUMOR/GRANULOSA CELL	4.570+	0.3707#
OVARIES	LIPOMA	2.190-	0.2743
OVARIES	LUTEOMA	7.810+	0.0170
UTERUS	SARCOMA/STROMAL CELL	0.012+	0.4996
UTERUS	LEIOMYOMA	1.019-	0.4653#
UTERUS	ADENOCARCINOMA	1.942-	0.3015
UTERUS	LEIOMYOSARCOMA	5.775+	0.1357
UTERUS	FIBROMA	7.758+	0.0188
UTERUS	GRANULAR CELL TUMOR	7.758+	0.0188
UTERUS	POLYP/STROMAL	15.578+	0.0778#
VAGINA	FIBROMA	2.282-	0.2709
PITUITARY GLAND	ADENOMA/P.DISTALIS	7.384-	0.2090#
THYROID (BOTH LOBES)	ADENOMA/FOLLICULAR	4.642-	0.1977
PARATHYROID GLANDS	ADENOMA	4.745-	0.1894
ADRENAL CORTEX	ADENOMA/B-CELL	7.758+	0.0188
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.	2.242-	0.2743
ADRENAL CORTEX	ADENOMA/A-CELL	7.627+	0.0222
ADRENAL MEDULLA	MEDULL.TUMOR/MALIGN.	2.242-	0.2743
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	2.306-	0.2676
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	17.653-	0.1075#
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	52.989-	0.0250#
SYSTEMIC NEOPLASMS	BONE MARROW LYMPHOMA	2.242-	0.2743

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~~C = 9/200~~
~~LD = 3/100~~
~~MD = 6/100~~
~~AD = 4/100~~

Tab. C.S.a.7. (cont.)

PATHOLOGY REPORT
STATISTICAL EVALUATION

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BOE PROJECT: G 70

TEST ARTICLE : SNO 919 CL 2 Y
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PATHOL. NO.: 91009 HHW
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

TREND TEST STATISTICS ON NEOPLASTIC LESIONS
COMBINED PREVALENCE AND DEATH RATE METHOD (PEYO ET AL., 1980)

DOSE GROUPS : G0, G1, G2, G3, G4
STATUS AT NECROPSY: K0 INCL. +
TIME INTERVAL FOR INCIDENTAL ANALYSIS: AD HOC RUN

SEX: FEMALE

ORGAN/TISSUE	TYPE OF NEOPLASM	TREND	P-VALUE
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	8.252-	0.2420#
SYSTEMIC NEOPLASMS	MAST CELL TUMOR	7.758+	0.0188
SYSTEMIC NEOPLASMS	MYELOID LEUKEMIA	2.360-	0.2676
MESENT. LYMPH NODE	HEMANGIOMA	2.464-	0.2483
HARDERIAN GLANDS	ADENOCARCINOMA	1.976-	0.2981
HARDERIAN GLANDS	ADENOMA	12.725-	0.0778#
SKIN	HEMANGIOSARCOMA	2.038-	0.2946
SKIN	SARCOMA/OSSIFYING	2.362-	0.2644
SKIN	LEIOMYOSARCOMA	3.160+	0.3372
SKIN	CARCINOMA/BASAL CELL	2.075-	0.2912
SKIN	HEMANGIOMA	1.942-	0.3015
SKIN	CARCINOMA/SQUAMOUS	2.014-	0.2946
SKIN	SCHWANNOMA	2.333-	0.2676
SKIN	SARCOMA/UNDIFFERENT.	0.274-	0.4705
BODY CAVITIES	SARCOMA/UNDIFFERENT.	5.318+	0.1587

POOLED ORGANS/FINDINGS

SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA		
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA		
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA		
SYSTEMIC NEOPLASMS	BONE MARROW LYMPHOMA		
		75.982-	U:0059#

POOLED ORGANS/FINDINGS

		TREND	P-VALUE
ADRENAL CORTEX	ADENOMA/B-CELL		
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.		
ADRENAL CORTEX	ADENOMA/A-CELL		
		13.142+	0.0212

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PATHDATA SYSTEM Vb3.6

TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

SEX: MALES

ORGAN/TISSUE	TYPE OF NEOPLASM	P-VALUE
LUNGS	ADENOMA	0.4296
LIVER	ADENOMA/HEPATOC.	0.0663
LIVER	HEMANGIOSARCOMA	0.6462
TESTES	LEYDIG CELL TUMOR	0.1536
ADRENAL CORTEX	ADENOMA/B-CELL	0.5593
ADRENAL CORTEX	ADENOMA/B-CELL/EXTD.	0.0720
ADRENAL CORTEX	ADENOMA/Z.FASCICUL.	0.5123
ADRENAL CORTEX	ADENOMAS/TOTAL	0.1450
HARDERIAN GLANDS	ADENOMA	0.3355
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	0.8941
SYSTEMIC NEOPLASMS	NONSPECIF. LYMPHOMA	-
SYSTEMIC NEOPLASMS	NONTHYMIC LYMPHOMA	0.5578
SYSTEMIC NEOPLASMS	MALIGN. LYMPHOMA/TOTAL	0.5740
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	0.0018

SEX: FEMALES

LUNGS	ADENOMA	0.1048
OVARIES	TUMOR/GRANULOSA CELL	0.5743
UTERUS	POLYP/STROMAL	0.3589
UTERUS	LEIOMYOMA	0.9954
PITUITARY GLAND	ADENOMA/P.DISTALIS	0.1239
HARDERIAN GLANDS	ADENOMA	0.1154
SYSTEMIC NEOPLASMS	THYMIC LYMPHOMA	0.0715
SYSTEMIC NEOPLASMS	NONSPEC. LYMPHOMA	-
SYSTEMIC NEOPLASMS	NON-THYMIC LYMPHOMA	0.6700
SYSTEMIC NEOPLASMS	BONE MARROW LYMPHOMA	-
SYSTEMIC NEOPLASMS	MALIGN. LYMPHOMA/TOTAL	0.0204
SYSTEMIC NEOPLASMS	HISTIOCYTIC SARCOMA	0.9139

NOTE: STATISTICAL CALCULATION WAS PERFORMED ONLY IF THE NUMBER OF NEOPLASMS EXCEEDED 5% PER DOSE GROUP AND SEX.

END OF REPORT SECTION

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Tab. C.5.a.8.

PATHOLOGY REPORT
SUMMARY TABLES

PAGE : 24/ 781
BOE PROJECT: G 70

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SPONSOR : BOEHRINGER INGELHEIM KG

PATHOL. NO.: 91009 HAW
DATE : 11-MAY-93
PATHDATA SYSTEM Vb3.6

EVALUATION OF NEOPLASTIC LESIONS
STATUS AT NECROPSY: KO, INCL. +

NUMBER OF ANIMALS WITH NEOPLASMS:

DOSE GR:	G0		G4		G1		G2		G3	
	M	F	M	F	M	F	M	F	M	F
NO. EXAM:	50	50	50	50	50	50	50	50	50	50
NO. AFF.:	40	35	30	33	32	37	23	27	24	30
%	80.0	70.0	60.0	66.0	64.0	74.0	46.0	54.0	48.0	60.0

DOSE GR:	TOTAL	
SEX :	M	F
NO. EXAM:	250	250
NO. AFF.:	149	162
%	59.6	64.8

NUMBER OF ANIMALS WITH MORE THAN ONE PRIMARY NEOPLASM:

DOSE GR:	G0		G4		G1		G2		G3	
	M	F	M	F	M	F	M	F	M	F
NO. EXAM:	50	50	50	50	50	50	50	50	50	50
NO. AFF.:	24	12	14	15	11	15	7	10	9	5
%	48.0	24.0	28.0	30.0	22.0	30.0	14.0	20.0	18.0	10.0

DOSE GR:	TOTAL	
SEX :	M	F
NO. EXAM:	250	250
NO. AFF.:	65	57
%	26.0	22.8

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Tab. C.5.a. 8. (cont.)

NUMBER OF ANIMALS WITH METASTASES:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
NO. EXAM:	50	50	50	50	50	50	50	50	50	50
NO. AFF.:	0	0	0	1	0	1	0	0	0	1
% :	0.0	0.0	0.0	2.0	0.0	2.0	0.0	0.0	0.0	2.0

DOSE GR: TOTAL
SEX : M F

NO. EXAM: 250 250
NO. AFF.: 0 3
% : 0.0 1.2

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NUMBER OF PRIMARY NEOPLASMS/GROUP/SEX:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
PRIM. T.:	76	55	46	52	46	56	32	39	35	35

DOSE GR: TOTAL
SEX : M F

PRIM. T.: 235 237

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NO. OF BENIGN, UNCLASSIFIED, MALIGN. NEOPLASMS/GROUP/SEX:

DOSE GR:	G0		G4		G1		G2		G3	
SEX :	M	F	M	F	M	F	M	F	M	F
BENIGN :	61	23	33	23	28	28	18	21	25	19
UNCLASS.:	0	0	0	0	0	0	0	0	0	0
MALIGN.:	15	32	13	29	18	28	14	18	10	16

DOSE GR: TOTAL
SEX : M F

BENIGN : 165 114
UNCLASS.: 0 0
MALIGN.: 70 123

C.5.b. Two-Year Rat Carcinogenicity Study

Conducted by : Boehringer Ingelheim KG
Depts. of Experimental Pathology and Toxicology and
Pharmacokinetics and Metabolism
Research and Development Coordination
Muttensz, Switzerland

Document #(s): BI Document U94-0250
Upjohn TR 7219-94-068

Sponsor Volumes: 1.49-1.54

This study complied with GLP

Summary:

Pramipexole was administered in the diet at doses of 0.3, 2.0, and 8.0 mg/kg/day to Wistar rats (50/sex/dose group, 100/sex/control) for two years. Toxicokinetic analyses were conducted in satellite groups at weeks 2, 50, and 100.

Mortality occurred in all treatment groups at various times during the study; there were no clear drug-related effects. The highest percentage of mortality was 40% in LDF. Body weight gain was significantly reduced at most time points in all three treatment groups. In MDF and HDF, body weight gain was reduced by 22 and 28%, respectively, at the end of the study. Other clinical observations included increased spontaneous activity in HDF, decreased food intake in males and LDF, and increased food intake in MDF and HDF.

The only neoplastic lesion that occurred at a higher incidence rate in PPX-treated rats were Leydig cell adenomas in MD (2.0 mg/kg/day) and HD (8.0 mg/kg/day) males. Leydig cell hyperplasia also occurred in MD and HD rats. Drug-related decreases in the incidence mammary gland neoplasia (MDF, HDF), benign adrenal medullary neoplasms (LDF, MDF, HDF), and pituitary adenomas (MD, HD of both sexes) were observed. Adrenal medullary hyperplasia was also reduced in MDF and HDF. Non-neoplastic changes in females were enlarged corpora lutea (HD rats), uterine lesions and hemorrhage (MD and HD), alterations in mammary gland patterns from female-like to male/female-like (MD and HD), and diffuse hepatocellular fatty changes (MD and HD). Retinal degeneration occurred in MD and HD groups of both sexes.

Toxicokinetic analyses indicated that in the low dose group, plasma exposure levels 2 hrs after light onset were lower the steady-state C_{max} in humans receiving the projected maintenance dose of 1.5 mg PPX, t.i.d., 2-5 fold higher than the human C_{max,s} after the intermediate dose, and 10-30 fold higher after the highest dose.

The proposed mechanism for the neoplastic and non-neoplastic lesions in reproductive and endocrine tissues is PPX-induced inhibition of prolactin secretion as demonstrated at week 60 and 69 (ca. 10-fold decrease in females, 100-fold decrease in males). In males, reductions in serum prolactin purportedly lead to a down-regulation of LH receptors. This triggers a compensatory increase in LH production and release leading to Leydig cell

hyperplasia and adenomas. The sponsor cites a study by Rao et al. (1984) which demonstrates that the dopamine agonist bromocriptine elevates LH; however, no evidence for a similar action of PPX on serum LH or LH receptor number was provided. Nonetheless, the finding is suggested to be of questionable relevance to humans given the high background incidence of this tumor in rats (as demonstrated in this experiment), and since several widely-used compounds also produce Leydig cell tumors in rats but are not known to do so in humans (cimetidine, hydralazine, vidarabine, israpidine). Additional evidence that Leydig cell adenomas may be species-specific is that a similar tumor was not observed in the mouse. The reduction in serum prolactin is also suggested to underlie the decreased incidence of pituitary adenomas, since prolactin normally stimulates anterior pituitary cell proliferation. The decreased incidence of benign adrenal medullary neoplasia is suggested to result from a dopamine receptor-mediated inhibition of chromaffin cell catecholamine release which decreases the proliferative potency of the chromaffin cells.

The corpora lutea enlargement, uterine changes, and changes in the glandular pattern of the mammary glands in PPX-treated female rats were also observed in the one year rat study. The sponsor has presented an argument to discount the potential human relevance of this finding based on the divergent effects of prolactin in rats and humans. In the rat, prolactin is luteolytic, and in its absence non-functional corpora lutea persist (and enlarge). In addition, prolactin stimulates progesterone secretion in the rat, and a reduction in the prolactin-progesterone stimulus results in unopposed actions of estrogen. Aging rats are susceptible to a chronic estrogenic state which leads to the uterine changes. However, this does not occur in aging women due to ovarian involution. Once again these proposed pathways in rats should be considered speculative in the case of PPX since studies of PPX-induced hormonal changes were not presented to support these arguments. The role of PPX inhibition of prolactin secretion in the mammary gland tissue pattern change was described in the one-year rat study.

Retinal degeneration in both male and female rats from the mid- and high-dose groups was the most notable non-neoplastic finding of this study. Follow-up studies to address this issue have been conducted by the sponsor, submitted to the IND, and reviewed. These studies will be independently reviewed by an FDA consultant (Dr. Tim O'Neill). The only noteworthy aspect of the current NDA submission that needs to be addressed as a part of this review is related to dosage level/exposure. The sponsor minimizes the relevance of the retinal degeneration findings in the discussion since the doses at which the effects were observed were "between 20 and 80 times the intended therapeutic dose in man." Based on an expected $C_{max_{ss}}$ in humans of ng/ml , the exposure level in MD rats (ng/ml) is only times higher than this level.

Hepatocellular fatty changes (steatosis) were observed in PPX-treated females. These were characterized as either diffuse or restricted to zones 1 and 2. Increased incidences of diffuse changes were dose-dependent and statistically significant in the MD and HD groups. Fatty changes restricted to zones 1 and 2 occurred at a lower rate (Con=7%; LD=24%, MD=22%, LD=18%). The potential mechanism or significance of these findings were not discussed. However, in the 52-week rat study, PPX caused a dramatic dose-dependent reduction in serum cholesterol and triglycerides suggesting a possible interference with hepatic transport or mobilization by PPX. Since both the biochemical and histological changes were observed only in females, a hormonal-based mechanism may be responsible. A direct relationship between the biochemical and histological changes could not be established in

either study. In the 52-week study, steatosis (peripheral fatty changes) occurred in all treatment groups, but the biochemical changes were more clearly dose-dependent. Clinical chemistry was not analyzed in the two-year study. Finally, there was no clear relationship between steatosis and more severe liver histopathologies; the highest incidence of necrosis (multicellular) was in MD females.

In summary, the only potential tumorigenic effect of PPX identified in this study was the induction of Leydig cell adenomas in males, possibly through an indirect hormonal mechanism that is not clinically relevant. The marked impairment of body weight development in MDF and LDF interferes with the interpretation of this study, and no conclusions regarding the carcinogenicity of PPX in female rats can be drawn. The "No Effect" dose was considered to be 0.3 mg/kg/day, although a decrease in body weight gain was apparent at this dose.

Methods:

Dosages: 0.3, 2.0, 8.0 mg/kg/day PPX (Lot: Batch II)

Low dose is 3-4 fold higher than the ED₅₀ for anti-Parkinsonian effects in monkeys. It is 5-15 times higher than the expected human maintenance dose range of 1.5-4.5 mg/day (70 kg human). The high dose was selected as the highest tolerable dose given the duration of the study and the limitation of excessive CNS stimulation.

Route of Administration: Drug-in-diet

Species/Strain/Number: Rat/Wistar (Chbb:THOM)

250 males, 250 females for toxicology

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Group size and dosage:

Group	Dose mg/kg	Number of animals		Identity number
		males	females	
0 (control A)	0	50	50	0001-0050 0501-0550
1	0.3	50	50	1001-1050 1501-1550
2	2.0	50	50	2001-2050 2501-2550
3	8.0	50	50	3001-3050 3501-3550
4 (control B)	0	50	50	4001-4050 4501-4550

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Three satellite groups (5, 6 and 7) were used for toxicokinetic analyses. Blood was sampled from 5 rats/sex in each group on days 2 and 7 of weeks 2, 50 and 100.

Mean initial weights/age:

males: 144.8g / 39 days
females: 131.6g / 39 days

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Parameters monitored/Intervals:

Clinical - - daily
Body weight - weekly (wks 1-26), monthly (wks 27-104)
Food consumption - weekly
Water consumption - weekly (weeks 13, 26, 39, 52, 65, 78, 91, 104)
Effective dose - calculated weekly (wks 1-26); monthly thereafter
Hematology - done only prior to sacrifice
Prolactin measurements - by RIA in wks 60 and 69
Plasma Conc - in satellite groups as described above
Histopathology - on the following tissues:

The following organs were placed in 7.5% buffered formaldehyde solution for histological preparation:

Adrenal glands	Prostate gland
Aorta	Rectum
Brain	Salivary glands
Caecum	Seminal vesicle
Cervical lymph node	Skeletal muscle
Colon	Skin
Duodenum	Spinal cord
Eyes/Hardnerian glands ³⁾	Spleen
Femur/stifle joint (incl. bone marrow)	Sternum ¹⁾
Heart	Stomach
Ileum	Testes with epididymides ²⁾
Jejunum	Thymus gland
Kidneys	Thyroid gland
Larynx ¹⁾	Tongue
Liver	Trachea
Lungs	Urinary bladder
Mammary gland	Uterus with cervix
Mesenteric lymph node	Vagina
Oesophagus	Both pinnae with ear tattoo ¹⁾
Ovaries	
Pancreas	
Parathyroid glands	All gross lesions incl. tumours/suspected tumours and regional lymph nodes
Periph. (sciatic) nerve	
Pituitary gland	

1) = conserved but not prepared histologically.

2) = fixed in Bouin's solution.

3) = fixed in Heidenhein's Susa solution.

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Tissues were fixed in 7.5% formalin (except eyes and Harderian glands were fixed in Susa's solution, and the testes with epididymides in Bouin's solution), embedded in Paraplast, and stained with H/E. Aorta, heart, kidneys, liver, lungs, and gross lesion were also stained with Masson-Goldner's trichrome technique. Sectioning was as follows:

Adrenal glands (6), aorta (1), bone and bone marrow [femur] (1), brain [cerebrum, cerebellum] (2), cervix (1), epididymides (2), esophagus (1), eyes (2), Harderian glands (2), heart (1), kidneys (2), large intestine [cecum, colon, rectum] (3), liver (1), lungs (1), lymph nodes [cervical, mesenteric] (2), mammary gland area (1), optic nerves (2), ovaries (2), pancreas (1), parathyroids (6), pituitary gland (3), prostate (1), salivary glands [sublingual, submandibular] (2), sciatic nerve (2), seminal vesicle (1), skeletal muscle (1), skin (1), small intestine [duodenum, jejunum, ileum] (3), spinal cord [cervical, thoracic, lumbar] (3), spleen (1), stomach (1), testes (2), thymus (1), thyroid gland (2), tongue (1), trachea (1), urinary bladder (1), uterus (3), vagina (1), and all gross lesions.

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Statistics

Analyses of routine samples were by Bartlett's test, or one-way ANOVA and Newman-Keuls test.

Tumor-bearing animals were categorized according to Peto et al. (1980) (1: incidental; 2: probably incidental; 3: probably fatal; 4: fatal), and analyzed using the positive and negative trend tests with respect to dose, and test for heterogeneity. Only p-values <0.05 for rare neoplasms, and <0.01 for common neoplasms were considered statistically significant.

The Exact Log Rank test was also used for group comparisons only when the number of tumor-bearing animals in a group was greater than 2, and for between-group comparisons of the number of premature decedents.

Results:

Mortality: 40 males and 69 females died over the course of the study. Causes of death are in Table C.5.b.1.

Group Sex	Contr. A		Contr. B		1		2		3	
	m	f	m	f	m	f	m	f	m	f
Died	4	4	0	2	3	6	1	9	3	7
Sacr.	4	9	9	8	4	14	5	6	7	4
Total	8	13	9	10	7	20	6	15	10	11
†	16	26	18	20	14	40	12	30	20	22

11.1.

No clear time- or dose-relationship was evident to implicate PPX as a causative factor.

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Table. C.5.b.1. Causes of Death or Sacrifice:

Controls (A&B)

<u>Males</u>	<u>17 deaths</u>	<u>Females</u>	<u>23 deaths</u>
neoplasia	- 11	neoplasia	- 16
pneumonia	- 2	cong. heart failure	- 1
dermatitis	- 1	pyometra/pyometritis	- 3
renal failure	- 1	pneumonia	- 1
cong. heart failure	- 1	multicell. necrosis	- 1
undetermined	- 1	pyelonephritis	- 1

Low-Dose

<u>Males</u>	<u>7 deaths</u>	<u>Females</u>	<u>20 deaths</u>
neoplasia	- 3	neoplasia	- 11
myodegeneration	- 1	pyometra/pyometritis	- 5
pyelitis/cystitis	- 1	ovarian abscesses	- 2
pneumonia	- 1	cong. heart failure	- 1
undetermined	- 1	liver abscesses	- 1

Mid-Dose

<u>Males</u>	<u>6 deaths</u>	<u>Females</u>	<u>15 deaths</u>
neoplasia	- 2	neoplasia	- 6
myocarditis	- 1	pyometra/pyometritis	- 5
undetermined	- 3	pyelonephritis	- 2
		pneumonia	- 1
		multicellular necrosis-	1

High-Dose

<u>Males</u>	<u>10 deaths</u>	<u>Females</u>	<u>11 deaths</u>
neoplasia	- 8	neoplasia	- 2
pneumonia	- 2	pyometra/pyometritis	- 9

11.7

Clinical: increased activity - HDF

Body Weight Gain (Fig. c.5.b.1):

LDM - sig. decrease - weeks 1-12, 15, 19, 21-23, 25-82
M & HDM - sig. decrease - all time points except HDM at wks 90-106
LDF - sig. decrease - all time points except wks 14, 15, 90
M & HDF - sig. decrease - all time points

Food Intake (Fig. C.5.b.2):

Males - tendency for decrease; no sig. effect at end of study
LDF - tendency for decrease; no sig. effect at end of study
M & HDF - tendency for increase

Water Intake: No remarkable trends

Effective dose: The large ranges in means, particularly in females, are primarily the result of larger than intended intakes in the latter portion of the study (i.e., after week 74).

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SMD 919 CL2Y : 104 - WEEK - STUDY IN RATS
EFFECTIVE DOSE

SEX		INTENDED DOSE					
		0.30 MG/KG		2.0 MG/KG		8.0 MG/KG	
		MEAN	X	MEAN	X	MEAN	X
FEMALE	MIN	0.24	79.7	1.76	88.1	6.83	85.4
	MAX	0.38	127.6	2.62	131.1	10.27	128.3
MALE	MIN	0.26	87.9	1.66	83.2	6.45	80.6
	MAX	0.34	114.3	2.38	118.8	9.70	121.2

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Fig. C.5.b.1.

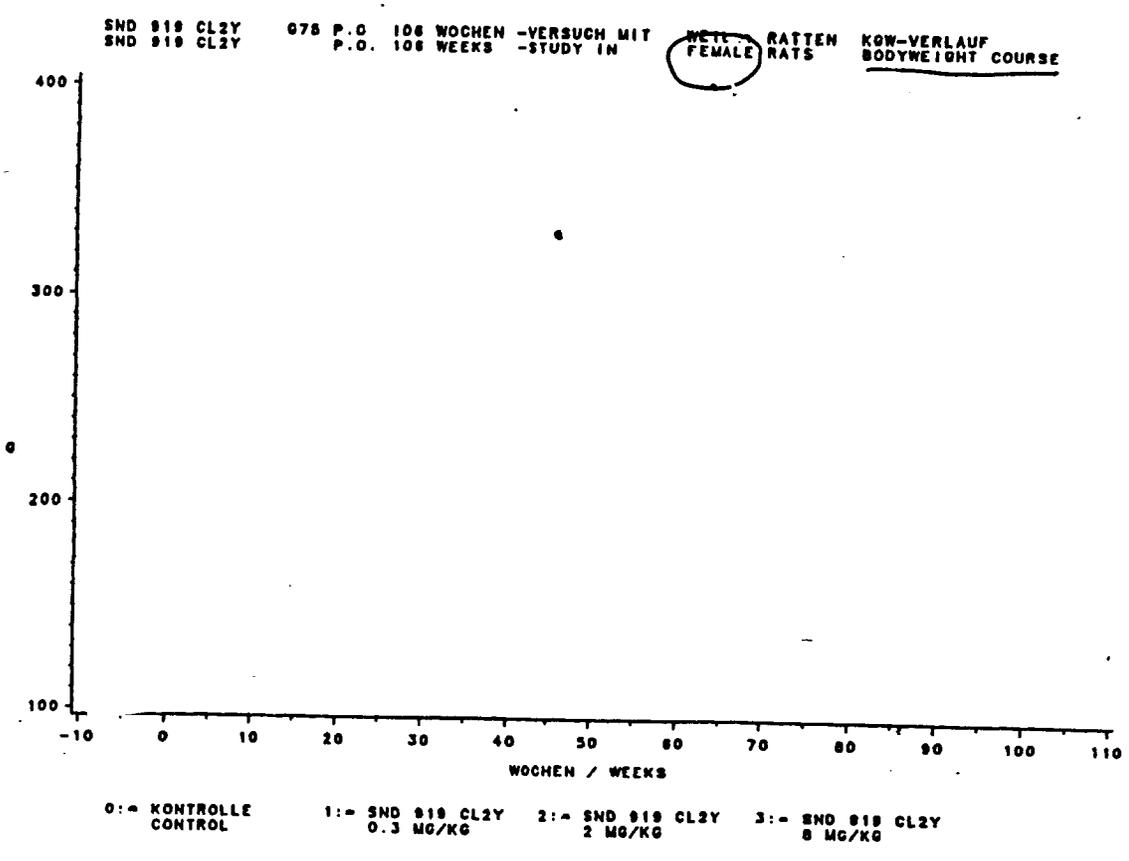
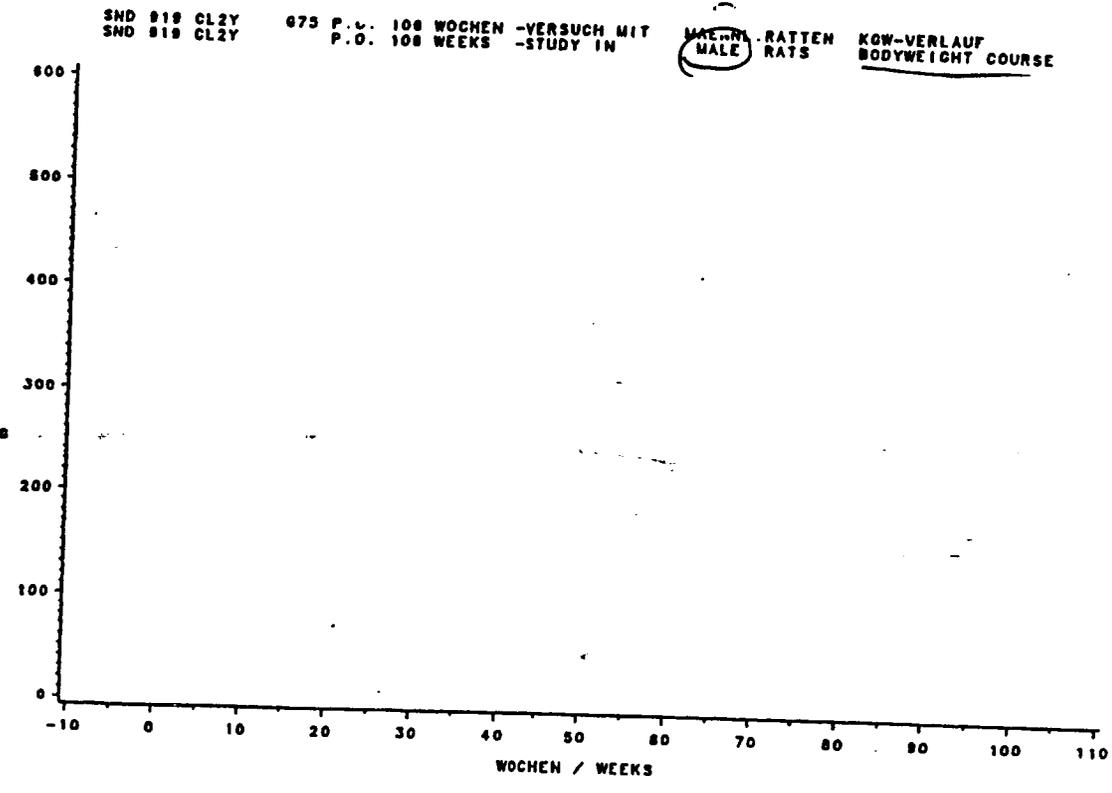


Fig. C.5.b.2.

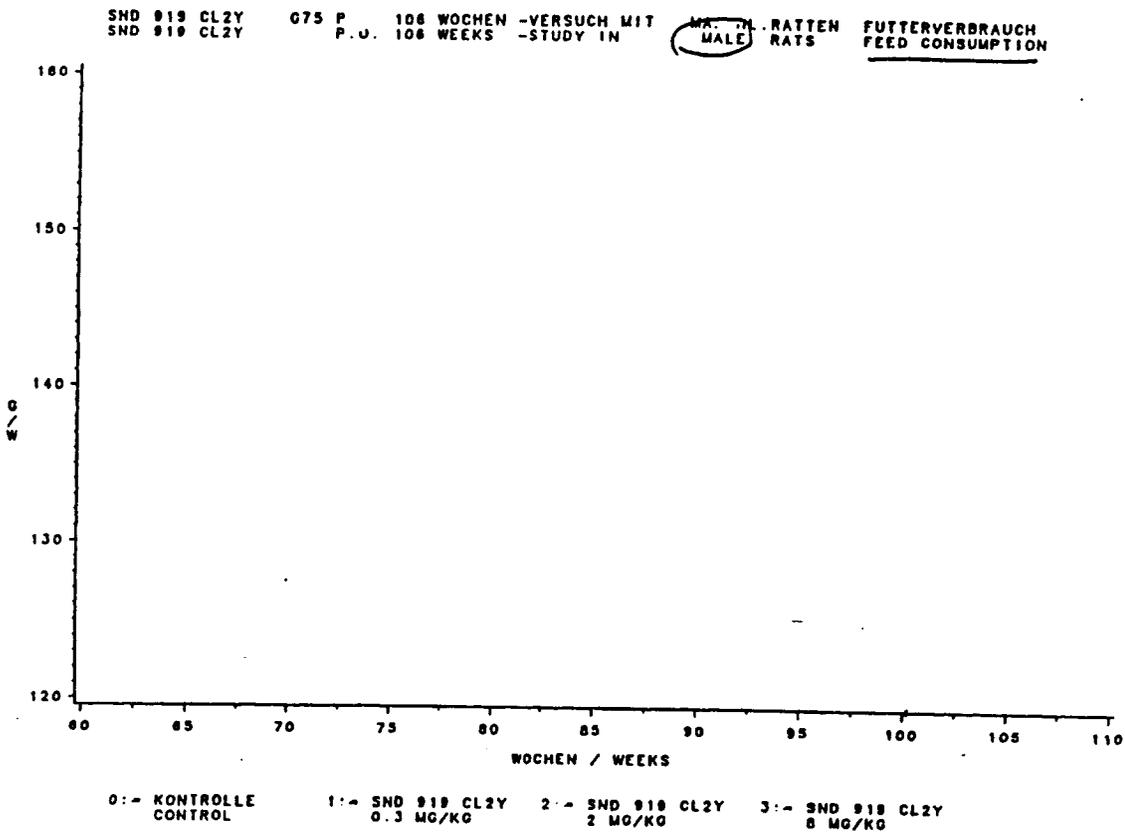
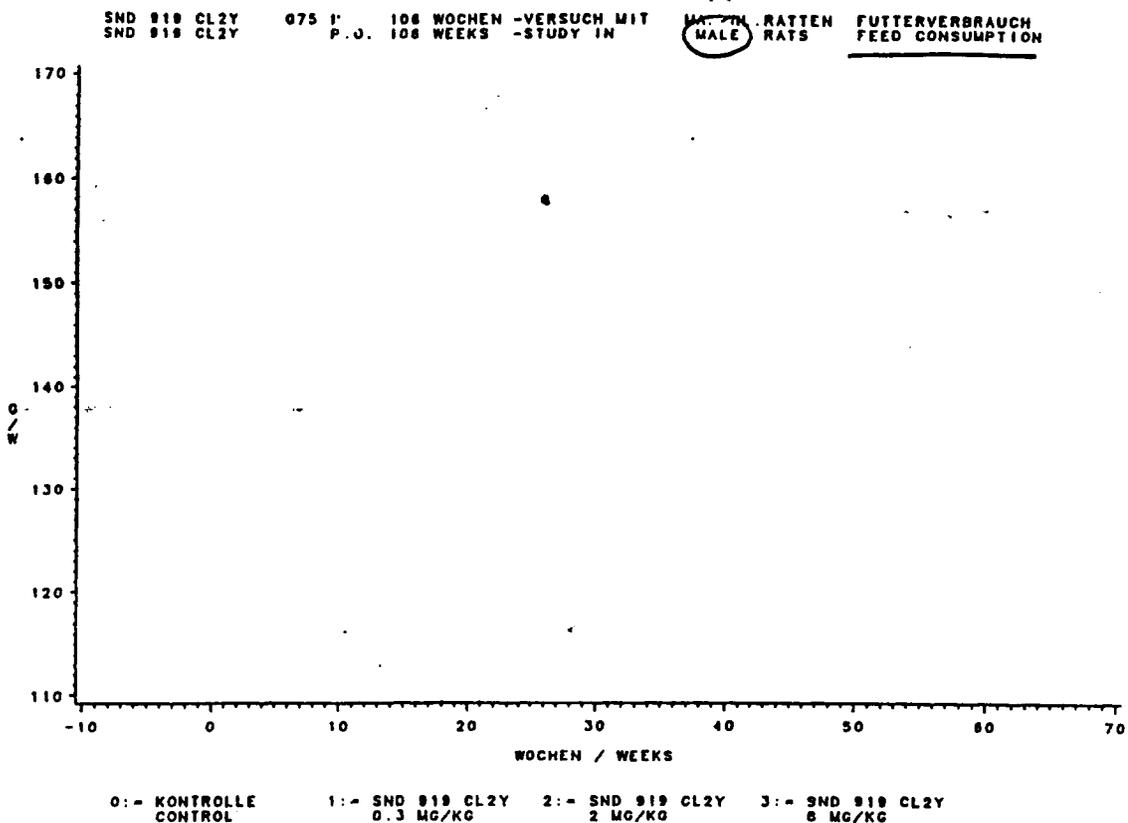
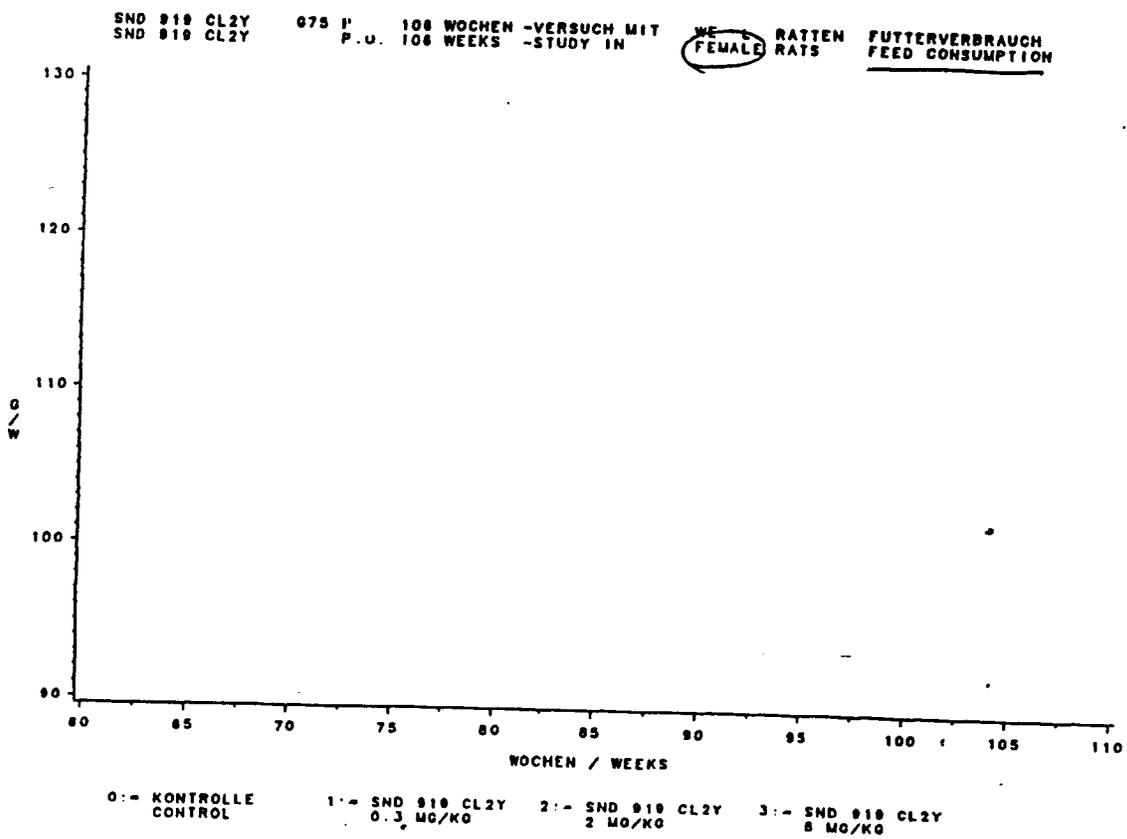
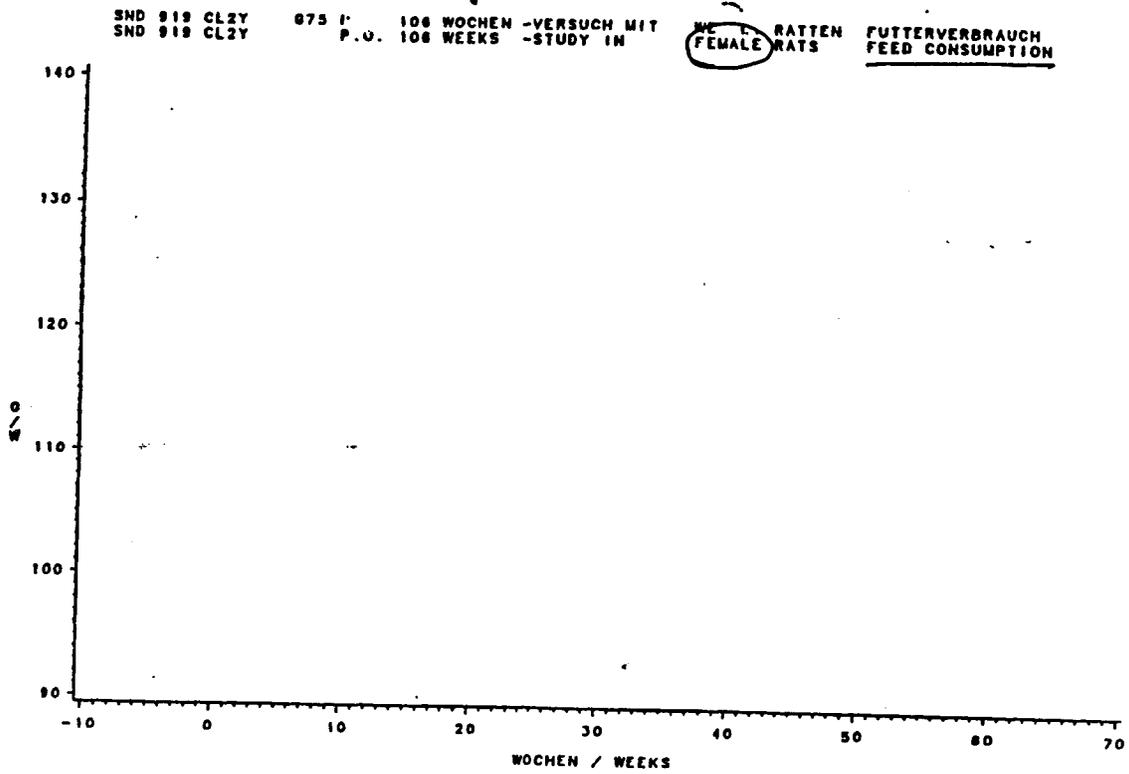


Fig. C.5.b.2. (cont.)



Hematology:

Group variations (at termination):

Statistically significant mean changes were noted on various parameters, but few clearly dose/drug-related effects were evident.

increased RBC	-	MDF, HDF
increased Hct	-	MDF, HDF
increased MCH	-	HDM
decreased MCH	-	HDF
increased MCHC	-	HDM
decreased MCHC	-	L, M & HDF
decreased eosinophils	-	L, M & HDF
decreased monocytes	-	M & HDF

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Individual variations (at termination):

increased WBCs	-	1 Con M, 1 Con F 1 LDM, 1 LDF 1 MDM 1 HDM
anemia, slight	-	5 Con M, 7 Con F 2 LDF 2 MDM 2 HDF
" , marked	-	1 MDF
polycythemia	-	1 Con M 1 MDM 1 HDM

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Individual variations (in moribund sacrifices) (Tab. C.5.b.2):

Control
Animals

animal no.	leucocytosis	relative		blasts	anaemia
		lymphocytosis	granulocytosis		
0514	•		•		•
0515	•		•		•••
0549	•		••		
4009	•		••		•••
4034	•••	•••			•
4047	•		monocytosis		
4535	•				•

LD

animal no.	leucocytosis	relative		blasts	anaemia
		lymphocytosis	granulocytosis		
1503	•		•		
1519	••				•••
1525	•		•		•
1534	•		•		•
1536	•••	••			•
1537	••		••		••
1543	•		•		

MD

animal no.	leucocytosis	relative		blasts	anaemia
		lymphocytosis	granulocytosis		
2005	••		••		•
2020	•		••		
2034	•		•		
2502	•		•		••
2507	•		•		••

HD

animal no.	leucocytosis	relative		blasts	anaemia
		lymphocytosis	granulocytosis		
3009	•		eosinophilia		
3023	•		••		
3024	•				•
3040	•				•
3505	••		••		•
3521	•				•
3536	•		•		•

In a further 11 animals without changes in the total white blood cell count, a slight (nos. 0520, 1036, and 3050), moderate (nos. 1011, 1510, 1548, 2048, 2530, and 3523), or marked (nos. 0013 and 4517) anaemia was established.

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Prolactin Measurements (Tab. C.5.b.3):

An inverse dose-relationship was observed at both time points in both sexes except for MDM at week 60, which had higher levels than control males.

Tab. C.5.b.3.

Influence of SND 919 CL 2 Y on Prolactin Levels (ng/ml)
(week 60)

Dose (mg/kg)		Male	Female
0 (control)	mean	108.03	166.44
	s.d.	48.64	117.19
	n	4	4
0.3	mean	30.68	141.33
	s.d.	12.36	158.43
	n	7 **	6
2.0	mean	134.60	34.35
	s.d.	54.37	27.04
	n	10	9 *
8.0	mean	< 0.39	15.87
	s.d.	-	9.53
	n	9 **	9 **

Influence of SND 919 CL 2 Y on Prolactin Levels (ng/ml)
(week 69)

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Dose (mg/kg)		Male	Female
Control	mean	66.98	251.64
	s.d.	28.38	103.41
	n	4	4
0.3	mean	37.56	136.86
	s.d.	28.77	76.26
	n	7 *	8
2.0	mean	<18.59	86.38
	s.d.	-	46.07
	n	9 *	9 *
8.0	mean	< 0.66	27.76
	s.d.	-	24.75
	n	7 **	10 **

Plasma Concentrations (Tab. C.5.b.4):

Increases in plasma concentrations were approximately dose-proportional. Levels at the 8.00 time-point (time of day) were higher than the 14.00 hr time-point. Measurements taken on different days within the same week did not appear to differ. There was a tendency for drug accumulation in males, but not females; this was particularly evident at week 100. There was no clear sex difference with the exception of the HD groups at week 100, where levels in males appeared to be higher.

(Note: There appears to be a discrepancy between the graphical and tabular data presentation. This likely occurred because 8 hr was used as a time point reference under two different scenarios - according to time of day (8.00 hr), and according to the number of hours after light onset (14.00 hr) (i.e., blood was collected at 8.00 hr (AM) - two hrs after light onset, and 8 hr after light onset - 14.00 hr). Analysis of the individual data indicates that the tabular presentation on pages 5/24/241-2 is the accurate presentation).

Table 5.E.9. Rat Mean Plasma Pramipexole Concentrations (ng/mL) in the 2-Year Carcinogenicity Study*

Sex	Dose (mg/kg)	Two Hours After Start of Light Phase					
		Week/Day					
		2/2	2/7	50/2	50/7	100/2	100/7
Female	0.3	2.39	1.96	1.86	1.66	4.52	3.64
	2.0	14.86	16.08	19.30	19.54	22.66	18.80
	8.0	77.53	103.11	80.25	76.43	65.81	70.79
Male	0.3	1.71	1.60	2.12	2.13	3.18	2.85
	2.0	15.03	13.13	20.16	18.51	27.14	22.97
	8.0	77.20	79.44	93.21	70.11	140.66	133.95

Table 5.E.9. Rat Mean Plasma Pramipexole Concentrations (ng/mL) in the 2-Year Carcinogenicity Study*

Sex	Dose (mg/kg)	Eight Hours After Start of Light Phase					
		Week/Day					
		2/2	2/7	50/2	50/7	100/2	100/7
Female	0.3	0.88	0.60	1.43	0.64	4.97	2.63
	2.0	3.73	7.09	6.73	5.93	28.10	19.50
	8.0	14.34	32.67	21.72	25.00	66.10	24.58
Male	0.3	0.34	0.75	0.96	1.03	1.51	1.98
	2.0	5.42	3.20	9.59	7.02	16.28	8.47
	8.0	24.59	25.23	57.09	47.30	65.52	47.17

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Pathology:

Non-neoplastic lesions

Aside from the retinal degeneration findings which are discussed in other portions of this review, the most significant findings were primarily in reproductive tissues, putatively due to the prolactin-inhibiting effects of PPX. Macroscopic lesions in treated females included enlarged or discolored ovaries, and uterine dilatation with hemorrhagic or watery contents. Microscopic alterations in these tissues were enlarged corpora lutea, and chronic suppurative lesions in the uterus. These lesions are suggested to result from a estrogen:progesterone imbalance in the absence of prolactin, which normally stimulates progesterone secretion. In addition, the glandular pattern of mammary gland tissue changes from a female-type tubuloalveolar pattern to a more male-like lobuloalveolar pattern in the absence of prolactin. The Leydig cell hyperplasia is also suggested to be linked to prolactin inhibition. In the absence of prolactin, LH receptors will down-regulate leading to compensatory increases in serum LH, and supposedly hypertrophy of Leydig cells (this is a speculative mechanism; a question that arises is how the Leydig cells respond to LH if the receptors are reduced in density). The reduced incidence of adrenal medullary hyperplasia is suggested to result from PPX-inhibition of catecholamine release from adrenal chromaffin cells.

Changes in the incidences of microscopic lesions were summarized as follows:

		Group/Incidence Rate (%)				
Lesion		0	4	1	2	3
I N C R E A S E	retinal degeneration (M)	0	0	0	51*	90*
	" (F)	2	0	0	21*	77*
	Leydig cell hyperplasia	70	78	80	92*	92*
	corpora lutea - enlarged	16	10	8	10	74*
	uterus, pyometra	4	10	14	24*	28*
	" , dilatation	18	47	34	58*	90*
	" , hemorrhage	2	10	18	24*	24*
	mammary gland - lobuloalveolar pattern (F)	0	0	0	0	34*
	mammary gland - mixed lobuloalveolar/tubuloalveolar pattern (F)	0	0	2	26	46
	hepatocellular fatty change (F)	6	4	4	34*	52*
vagina, blood	0	4	4	2	10	

D E C R	adrenal medullary hyperplasia (F)	47	57	55	30*	29*
	mammary gland - cystic change (F)	42	18	38	6*	0*
	pulmonary alveolar macrophages (F)	44	40	44	40	22*

Neoplastic Lesions:

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According to the sponsor's analysis, the only tumor that occurred with a higher frequency in PPX-treated animals than in controls was the Leydig cell adenoma. However, this tumor occurred with a high background incidence. The mechanism for increased incidence in PPX-treated animals is similar to that described for the Leydig cell hyperplasia.

Neoplasm	Group/Incidence rate (%)				
	0	4	1	2	3
Leydig cell adenoma - increase	26	18	34	44*	44*
mammary gland (all types) - decrease	14	8	12	0*	0*
pituitary adenoma - decrease (M)	8	20.4	12	0*	2*
" - " (F)	40	64	60	20.4 *	4.1*
benign adrenal medullary neoplasm - decrease (F)	38.8	65.3	32.7 *	8.7*	6.1*
thyroid C-cell carcinoma - decrease (F)	2	8	6	2	0
total # neoplasms - decrease (F)				*	*

The incidence of squamous papillomas in the cervix approached statistical significance by the Heterogeneity test ($p = 0.0548$), but the highest incidence of these tumors occurred at the lowest dose.

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Summary of Distribution of Neoplasms (Tab. C.5.b.6):

Name of company BOEHRINGER INGELHEIM KG		TABULATED STUDY REPORT ref. to III.E.210 — 3/9 — Page Number												
Name of finished product														
Name of active ingredient Prampexole (SND 919 CL 2 Y)														
ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data														
Ref. to document.: Volume: Page: to		Report date: 05.05.94 Number: G75		Addendum No.: Study period (years): 1989 - 1991										
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)			Frequency according to dose and sex (n)											
			(0) Contr. A		(4) Contr. B		(1)		(2)		(3)			
Biometrical evaluation yes < x > no < >			m		f		m		f		m		f	
Number of animals evaluated			50		50		50		50		50		50	
Organ	Identification of the tumour													
BRAIN	GRANULAR CELL TUMOUR		1	1	-	-	-	2	1	-	-	-	-	-
	OLIGODENDROGLIOMA		-	1	-	-	1	-	-	-	-	-	-	-
LUNGS	BRON./ALV. CARCINOMA		-	1	-	1	1	-	-	-	-	-	-	-
TONGUE	HEMANGIOMA		-	-	-	-	1	-	-	-	-	-	-	-
	GRANULAR CELL TUMOUR		-	-	-	1	-	-	-	-	-	-	-	-
	SARCOMA, NOS		-	-	-	-	-	-	-	-	-	1	-	-
JEJUNUM	LEIOMYOMA		-	-	-	-	-	-	-	1	-	-	-	-
	ADENOCARCINOMA		-	-	-	-	1	-	-	-	-	-	-	-
	LEIOMYOSARCOMA		-	-	-	1	-	-	-	-	-	-	-	-
ILEUM	LEIOMYOSARCOMA		-	-	-	-	1	-	-	-	-	-	-	-
STOMACH	ADENOCARCINOMA		1	-	-	-	-	-	-	-	-	-	-	-
CAECUM	ADENOCARCINOMA		-	-	-	-	-	-	1	-	-	-	-	-
LIVER	HEPATOC. ADENOMA		3	-	4	1	3	1	4	1	1	-	-	-
	CHOLANGIOMA		-	-	-	2	-	1	-	1	-	1	-	-
	HEPATOC. CARCINOMA		3	-	2	-	5	-	1	-	-	2	-	-
	CHOLANGIOPAPILLOMA		-	-	1	-	-	-	-	-	-	-	-	-
PANCREAS	ISLET-CELL ADENOMA		3	-	-	-	-	-	1	-	-	-	-	-
	ACINAR CARCINOMA		-	-	-	-	-	1	-	-	-	-	-	-

* P < 0.05 ** P < 0.01

1-1

Name of company BOEHRINGER INGELHEIM KG		TABULATED STUDY REPORT													
Name of finished product															
Name of active ingredient Pramipexole (SND 919 CL 2 Y)															
		ref. to III.E.210													
		4/9													
		Page Number													
ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data															
Ref. to document.: Volumes: Page: to Addendum No.:															
Report date: 05.05.94 Number: G75 Study period (years): 1989 - 1991															
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)						Frequency according to dose and sex (n)									
Biometrical evaluation yes <x> no <>						(0)		(4)		(1)		(2)		(3)	
						Contr. A		Contr. B							
						m	f	m	f	m	f	m	f	m	f
Number of animals evaluated						50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour														
KIDNEYS	TUBULAR ADENOMA					-	1	-	-	-	-	-	-	1	-
	NEPHROBLASTOMA					1	-	-	-	-	-	-	-	-	-
	LIPOSARCOMA					-	1	1	-	-	-	-	-	-	-
URINARY BLADDER															
	TRANSIT. PAPILLOMA					-	2	-	1	-	-	-	1	1	1
	SQUAMOUS PAPILLOMA					-	-	-	-	-	-	-	-	-	1
	TRANSIT. CARCINOMA					-	-	-	-	-	-	1	-	1	-
SQUAMOUS CARCINOMA					1	-	-	-	-	-	-	-	-	-	
TESTES	LEYDIG CELL ADENOMA**					13	-	9	-	17	-	22	-	22	-
OVARIES	GRANULOSA CELL TUMOR (B)					-	5	-	1	-	1	-	1	-	1
	THECA CELL TUMOR					-	-	-	1	-	2	-	1	-	-
	LUTEOMA					-	-	-	4	-	-	-	1	-	-
	CARCINOMA, NOS					-	-	-	-	-	-	-	1	-	-
UTERUS	ADENOMA					-	-	-	1	-	-	-	-	-	-
	LEIOMYOMA					-	-	-	-	-	-	-	-	-	1
	HEMANGIOMA					-	-	-	-	-	-	-	2	-	1
	GRANULAR CELL TUMOR					-	-	-	1	-	1	-	-	-	-
	ADENOCARCINOMA					-	2	-	2	-	2	-	2	-	1
	HEMANGIOSARCOMA					-	-	-	1	-	-	-	3	-	1

* P < 0.05 ** P < 0.01 (positive trend)

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Name of company BOEHRINGER INGELHEIM KG		TABULATED STUDY REPORT		ref. to III.E.210		5/9 Page Number								
Name of finished product														
Name of active ingredient Pramipexole (SND 919 CL 2 Y)														
ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data														
Ref. to document.: Volume:		Page:		to		Addendum No.:								
Report date: 05.05.94		Number: G75		Study period (years): 1989 - 1991										
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)					Frequency according to dose and sex (n)									
					(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
Biometrical evaluation yes < α > no < >					m	f	m	f	m	f	m	f	m	f
Number of animals evaluated					50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour													
UTERUS	LEIOMYOSARCOMA				-	-	-	-	1	-	-	-	-	1
CERVIX	SQUAMOUS PAPILLOMA				-	1	-	1	-	5	-	3	-	1
	STROMAL SARCOMA				-	3	-	1	-	3	-	4	-	1
	SQUAMOUS CARCINOMA				-	-	-	1	-	-	-	-	-	-
PIUITARY GLAND	ADENOMA m: **; f: ***				4	20	10	32	6	30	-	10	1	2
THYROID GLAND	FOLLICULAR ADENOMA				-	-	1	-	-	-	-	-	-	1
	C CELL ADENOMA				3	5	2	7	2	4	5	1	3	9
	GANGLIONEUROMA				1	-	-	-	-	-	-	-	-	-
	FOLLICULAR CARCINOMA				-	-	-	1	-	1	1	-	-	-
	C CELL CARCINOMA f: *				2	1	2	4	3	3	3	1	1	-
PARA- THYROID GLANDS	ADENOMA				-	1	2	2	2	3	1	-	1	-
ADRENAL CORTEX	ADENOMA				1	4	1	-	1	-	-	2	-	1
	CARCINOMA				1	-	-	-	-	-	-	1	-	1

* P < 0.05 ** P < 0.01 *** P < 0.001 (negative trend)

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Tab. C.5.b.6 (cont.)

TR No. 7219-94-068

U94-0250

Name of company BOEHRINGER INGELHEIM KG		TABULATED STUDY REPORT ref. to III.E.210 —6/9— Page Number											
Name of finished product													
Name of active ingredient Pramipexole (SND 919 CL 2 Y)													
ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data													
Ref. to document.: Volume: Page: to		Addendum No.:		Report date: 05.05.94 Number: G75 Study period (years): 1989 = 1991									
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <α> no < >				Frequency according to dose and sex (n)									
				(0) Contr. A		(4) Contr. B		-(1)		(2)		(3)	
				m	f	m	f	m	f	m	f		
Number of animals evaluated				50	50	50	50	50	50	50	50		
Organ	Identification of the tumour												
ADRENAL													
MEDULLA	MEDULLARY TUMOUR (B) f: ***			10	19	13	32	7	16	9	4	6	3
	MEDULLARY TUMOUR (M)			2	-	2	1	1	-	-	-	1	-
THYMUS	THYMOMA			-	-	-	-	-	1	-	-	-	-
MESENT.													
Lymph Node	HEMANGIOMA			-	-	5	1	2	-	3	1	4	-
HEMOLYMPH.													
SYSTEM	HISTIOCYTIC SARCOMA			-	1	1	1	-	1	-	1	-	-
	MALIGNANT LYMPHOMA			3	1	8	4	6	3	1	1	4	3
SPLEEN	HEMANGIOSARCOMA			1	1	-	1	-	1	1	-	2	-
SUBLINGUAL													
GLAND	ACINAR CARCINOMA			-	-	-	-	-	1	-	-	-	-
MAMMARY													
GLAND AREA	FIBROADENOMA			-	5	-	2	-	2	-	-	-	-
	ADENOMA			-	1	-	-	-	-	-	-	-	-
	PAPILL. CYSTADENOMA			-	-	-	-	-	1	-	-	-	-
	CARCINOMA			-	1	-	2	-	3	-	-	-	-
BONE	GRANULAR CELL TUMOUR			-	1	-	-	-	-	-	-	-	-
	SCHWANNOMA (M)			-	-	-	-	-	-	-	-	1	-

* P < 0.05 ** P < 0.01 *** P < 0.001 (negative trend)

180a

Name of company BOEHRINGER INGELHEIM KG		TABULATED STUDY REPORT		ref. to III.E.210		7/9		Page Number						
Name of finished product														
Name of active ingredient Pramipexole (SND 919 CL 2 Y)														
ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data														
Ref. to document.: Volume: Page: to Addendum No.:		Report date: 05.05.94 Number: G75 Study period (years): 1989 - 1991												
Number of tumours in all animals which were evaluated (without consideration of the causes and relevance)					Frequency according to dose and sex (n)									
					(0) Contr. A		(4) Contr. B		(1)		(2)		(3)	
Bimmetrical evaluation yes < > no < >					m	f	m	f	m	f	m	f	m	f
Number of animals evaluated					50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour													
BONE														
MARROW	HEMANGIOSARCOMA				-	-	1	-	-	-	-	-	-	-
SUBMANDIB. GLAND	SARCOMA, NOS				-	-	2	-	-	-	-	-	-	-
SKIN	KERATOACANTHOMA				2	-	2	-	1	-	-	-	-	-
	TRICHOFOLLICULOMA				-	-	1	-	-	-	-	-	-	-
	SEBACEOUS ADENOMA				-	-	1	-	-	-	-	-	-	-
	TRICHOLEMOMA				-	-	-	-	-	-	1	-	-	-
	LIPOMA				-	-	1	-	-	-	-	-	-	-
	FIBROMA				1	-	1	-	1	-	-	-	-	-
	SQUAMOUS CARCINOMA				-	-	-	-	-	1	-	-	2	-
	BASAL CELL CARCINOMA				-	-	1	-	2	-	-	-	-	2
	SEB/SQUAM. CARCINOMA				1	-	-	-	-	1	-	-	-	-
	SCHWANNOMA (N)				-	-	-	-	-	-	-	-	2	-
	HEMANGIOSARCOMA				-	-	1	-	-	-	1	-	1	-
	MAST CELL TUMOUR				-	-	-	-	-	-	-	-	1	-
	SARCOMA, NOS				-	-	1	-	-	-	-	-	1	-
FIBROSARCOMA				-	-	-	-	-	1	-	-	-	-	

* P < 0.05 ** P < 0.01

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TREND TEST STATISTICS ON NEOPLASTIC LESIONS
P VALUES FOR POSITIVE AND NEGATIVE TRENDS

DOSE GROUPS	: 0, 1, 2, 3, 4	SEX: MALE	
STATUS AT NECROPSY: KD INCL. +			
ORGAN/TISSUE	TYPE OF NEOPLASM	POSITIVE TREND	NEGATIVE TREND
LIVER	HEPATOC. ADENOMA	-	0.1236
LIVER	HEPATOC. CARCINOMA	-	0.2608
PANCREAS	ISLET-CELL ADENOMA	-	0.1567
TESTES	LEYDIG CELL ADENOMA	0.0057	-
PITUITARY	ADENOMA	-	0.0066
THYROID GLAND	C CELL ADENOMA	0.3635	-
THYROID GLAND	C CELL CARCINOMA	-	0.2286
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	-	0.1110
ADRENAL MEDULLA	MEDULLARY TUMOR (M)	-	0.2998
MESENT. LYMPH NODE	HEMANGIOMA	0.1590	-
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	-	0.2715

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TREND TEST STATISTICS ON NEOPLASTIC LESIONS
P VALUES FOR POSITIVE AND NEGATIVE TRENDS

DOSE GROUPS	: 0, 1, 2, 3, 4	SEX: FEMALE	
STATUS AT NECROPSY: KD INCL. +			
ORGAN/TISSUE	TYPE OF NEOPLASM	POSITIVE TREND	NEGATIVE TREND
OVARIES	GRANULOSA CELL TUMOR	-	0.1607
OVARIES	LUTEOMA	-	0.1026
CERVIX	SQUAMOUS PAPILLOMA	-	0.2051
CERVIX	STROMAL SARCOMA	-	0.2054
PITUITARY	ADENOMA	-	< 0.0001
THYROID GLAND	C CELL ADENOMA	0.0858	-
THYROID GLAND	C CELL CARCINOMA	-	0.0382
PARATHYROID GLANDS	ADENOMA	-	0.0558
ADRENAL CORTEX	ADENOMA	-	0.3407
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	-	< 0.0001
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	0.4648	-
MAMMARY GLAND AREA	FIBROADENOMA	-	0.0234
MAMMARY GLAND AREA	CARCINOMA	-	0.0566
MAMMARY GLAND AREA	(COMBINED NEOPLASMS)	-	0.0032
UTERUS	HEMANGIOSARCOMA	0.3030	-

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TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

		SEX: MALE
ORGAN/TISSUE	TYPE OF NEOPLASM	P- VALUE
LIVER	HEPATOC. ADENOMA	0.5938
LIVER..	HEPATOC. CARCINOMA	0.3381
PANCREAS	ISLET-CELL ADENOMA	0.4029
TESTES	LEYDIG CELL ADENOMA	0.0100
PITUITARY	ADENOMA	0.0071
THYROID GLAND	C CELL ADENOMA	0.5848
THYROID GLAND	C CELL CARCINOMA	0.7685
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	0.3218
ADRENAL MEDULLA	MEDULLARY TUMOR (M)	0.4930
MESENT. LYMPH NODE	HEMANGIOMA	0.7732
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	0.2421

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TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

		SEX: FEMALE
ORGAN/TISSUE	TYPE OF NEOPLASM	P- VALUE
OVARIES	GRANULOSA CELL TUMOR	0.5104
OVARIES	LUTEOMA	0.3011
UTERUS	HEMANGIOSARCOMA	0.1430
CERVIX	SQUAMOUS PAPILLOMA	0.0548
CERVIX	STROMAL SARCOMA	0.4969
PITUITARY	ADENOMA	< 0.0001
THYROID GLAND	C CELL ADENOMA	0.0723
THYROID GLAND	C CELL CARCINOMA	0.2787
PARATHYROID GLANDS	ADENOMA	0.0755
ADRENAL CORTEX	ADENOMA	0.4655
ADRENAL MEDULLA	MEDULLARY TUMOR (B)	< 0.0001
SYSTEMIC NEOPLASMS	MALIGNANT LYMPHOMA	0.7136
MAMMARY GLAND AREA	FIBROADENOMA	0.0632
MAMMARY GLAND AREA	CARCINOMA	0.0887