CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

PHARMACOLOGY REVIEW(S)

Executive CAC
October 8, 1996

Committee members:
Joseph DeGeorge, Ph.D., Chair (HFD-024)
Joseph Contrera, Ph.D. (HFD-900)
Charles Resnick, Ph.D., Rotating member (HFD-110)
Glenna Fitzgerald, Ph.D., Team leader (HFD-120)
Sharon Olmstead, Exec Sec (HFD-006, non-voting member)

NDA 20-667 (Steele; HFD-120)
Pramipexole
Upjohn

Mouse Carcinogenicity Study:
The sponsor submitted carcinogenicity study results from a 2-year study in mice using 0.3, 2, and 10 mg/kg/day. The basis of the HD selection was made on the findings from the 13-week toxicity study in which 8 and 13 mg/kg/day produced significant reduction in body weight gain. In the 2-year study, a significant decrease in body weight gain was report in the MD and HD groups. No significant tumor findings were reported in the mouse. The sponsor provided full histology on all dose groups.

Committee Recommendations:
The committee concurred with the dose selection and study design of the carcinogenicity study in the mouse. The tumor findings were adequately addressed. In response to discussion on the effects of treatment on body weight, the committee recommended that if relative systemic exposure is provided in the labeling then all dose groups should be included in the description.

Rat Carcinogenicity Study:
The sponsor submitted carcinogenicity study results from a 2-year study in rats using 0.3, 2, and 8 mg/kg/day. The HD selection was based on the body weight gain decreases observed in the 13-week toxicity study using doses between 3 and 20 mg/kg/day. The severe body weight effects observed with the mouse were not seen in the rat. Significant findings using the trend test were reported in the males for Leydig cell adenomas by the company, but were reported as non-statistically significant but by the FDA statistician using p 0.005 as the cut off for a common tumor.

Committee Recommendations:
The committee concurred with the dose selection and study design of the carcinogenicity study in the rat. The committee recommended that the tumor findings in the male rat be reanalyzed by FDA statistician using pairwise comparison. Specifically, a request should be made to OEB to conduct a pairwise comparison of Leydig cell tumors for each control separately. (The analysis indicated significance compared to one control but not the other.)

/S/ 2/9/96

Joseph DeGeorge, Ph.D.
Chair, CAC
Draft for comment Nov. 13

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ON ORIGINAL

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT

FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET

NDA: 20667 **IND:** **DRUG CODE#:**
CAS#: 104632-26-0 **DATE:** 10/8/96
DIVISION(s): HFD-120
DRUG NAME(s): Pramipexole; SND 919 CL2Y;
IUPAC: (S)-2-Amino-4,5,6,7-tetrahydro-6-propylaminobenzothiazole dihydrochloride monohydrate
CAS: (S)-N6-Propyl-4,5,6,7-tetrahydro-2,6-benzothiazolediamine dihydrochloride, monohydrate
SPONSOR: Upjohn
LABORATORY: Boehringer-Ingelheim
P/T REVIEWER(s): Thomas Steele
P/T REVIEW DATE:
CARCINOGENICITY STUDY REPORT DATE: 5/5/94
THERAPEUTIC CATEGORY: Anti-Parkinson's Drug
PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: Dopamine antagonist

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date): No

MUTAGENIC/GENOTOXIC (y/n/equivocal/na; assay):

Negative in Ames test, SHE cell transformation assay, V79 gene mutation assay, *in vivo* micronucleus test, and chromosomal aberrations in CHO cells. A potential impurity was weakly positive in the Ames test, but this compound has not appeared in any clinical batches to date.

RAT CARCINOGENICITY STUDY (multiple studies? Std1;Std2 etc.):

RAT STUDY DURATION (weeks): 104
STUDY STARTING DATE: 5/23/89
STUDY ENDING DATE: 6/20/91
RAT STRAIN: Wistar (Chbb:THOM)
ROUTE: oral, in diet
DOSING COMMENTS:

No. Rats in Control1 (C1):	50/sex	**Control2 (C2):**	50/sex	
Low Dose (LD):	main: 50/sex;	TK:	5/sex	
Middle Dose (MD):	main: 50/sex;	TK:	5/sex	
High Dose (HD):	main: 50/sex;	TK:	5/sex	

ADDITIONAL CONSIDERATIONS:

Effect on Mortality:

No significant relationship of drug treatment with mortality was identified by the sponsor or the Agency's statistical reviewer (Roswitha Kelly). Survival rates were 80-83% in the male rat groups, and 60-77% in the female rat groups (see attached tables).

Table 1
INTERCURRENT MORTALITY RATES

	MALE RATS mg/kg/day			
Weeks	0	0.3	2.0	8.0
0- 52	2/99 (2%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
53- 78	1/97 (3%)	0/50 (0%)	2/49 (6%)	1/49 (4%)
79- 92	6/96 (9%)	2/50 (4%)	1/47 (8%)	2/48 (8%)
93-107	8/90 (17%)	5/48 (14%)	2/46 (12%)	6/46 (20%)
Term. Sac.	82/99 (83%)	43/50 (86%)	44/50 (88%)	40/50 (80%)

	FEMALE RATS mg/kg/day			
Weeks	0	0.3	2.0	8.0
0- 52	3/100 (3%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
53- 78	7/97 (10%)	2/49 (6%)	0/50 (0%)	3/49 (8%)
79- 92	5/90 (15%)	5/47 (16%)	7/50 (14%)	1/46 (10%)
93-107	8/85 (23%)	12/42 (40%)	7/43 (28%)	6/45 (22%)
Term. Sac.	77/100 (77%)	30/50 (60%)	36/50 (72%)	39/50 (78%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

The slight impairment of body weight development in males should not have negatively impacted tumor formation. However, the marked impairment in females at both the intermediate and high doses interferes with the interpretation the data. In the 13-week study used for dose-range selection, a dose of 4 mg/kg pramipexole impaired body weight development in both males and females by approximately 30%. Thus, a marked effect of 8 mg/kg should not have been unexpected.

Exposure Data:

Plasma concentrations were determined in satellite groups during weeks 2, 50, and 100 at 2 and 8 hrs after the onset of the light phase. Estimates of t_{max} for orally administered pramipexole in rats was [illegible]rs.

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

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	75.43	65.81	70.79
Male	0.3	1.71	1.60	2.12	2.13	3.18	2.85
	2.0	15.03	18.13	20.18	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[a]

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 (2.00-6.95)	7.09 (4.75-10.60)	6.73 (4.78-9.49)	5.93 (3.08-11.43)	26.10 (15.31-44.51)	19.50 (9.53-40.66)
	8.0	14.34	32.67	21.72	25.00	83.12	24.58
Male	0.3	0.34	0.75	0.96	1.03	1.51	1.38
	2.0	5.42	3.20	9.59	7.02	16.28	8.47
	8.0	24.59	25.23	57.09	47.80	65.52	47.17

MOUSE CARCINOGENICITY STUDY (multiple studies? Std1;Std2 etc.):

MOUSE STUDY DURATION (weeks): 105-106 weeks
STUDY STARTING DATE: 2/23/89
STUDY ENDING DATE: 1/3/91
MOUSE STRAIN: Chbb:NMRI
ROUTE: oral, in diet
DOSING COMMENTS:

No. Mice in Control1 (C1): 50 **Control2 (C2):** 50
Low Dose (LD): main: 50/sex; TK: 20/sex
Middle Dose (MD): main: 50/sex; TK: 16/sex
High Dose (HD): main: 50/sex; TK: 12/sex

MOUSE DOSE LEVELS (mg/kg/day):

Mouse LD: 0.3 mg/kg/day
Mouse MD: 2.0 "
Mouse HD: 10.0 "

Basis for Doses Selected (MTD; AUC ratio; saturation; maximum feasible):

The low dose was selected to correspond tc times the expected human dose at the time the study was initiated. It was approximately 3 times the ED_{50} for anti-parkinsonian activity in monkeys.

The high dose was selected on the basis of a 13-week study in which doses of 8 and 13 mg/kg markedly reduced body weight gain (by %).

Prior FDA Concurrence (Did/CAC)? (y/n;Date): none

MOUSE CARCINOGENICITY (negative; positive; MF; M; F):

Negative in both males and females.

MOUSE TUMOR FINDINGS:

None of the tumor findings exhibited a positive trend with dose according to analyses by the sponsor and by the Agency's statistical reviewer. **Negative** trends in tumor incidence were identified:

	Group/Incidence rate (%)				
Neoplasm	C1	C2	LD	MD	HD
malignant lymphoma (F)	46	42	32	22*	16*
adrenal cortical adenomas (M)	32	16	16	12	6*

Table 4

Results of Intercurrent Mortality Analyses

Male Mice

Groups Compared	Direction	Two-tailed P-Value of Test Cox	Kruskal/Wallis
C,L,M,H	pos	.067	.040*
C,L	pos	.012*	.011*
C,M	pos	.006**	.002**
C,H	pos	.011*	.005**
L,M	pos	.857	.507
L,H	neg	.882	.625
M,H	nrg	.982	.873

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Female Mice

Groups Compared	Direction	Two-tailed P-Value of Test Cox	Kruskal/Wallis
C,L,M,H	pos	.253	.205
C,L	pos	.153	.077
C,M	pos	.768	.607
C,H	pos	.163	.084
L,M	neg	.445	.314
L,H	pos	.984	.999
M,H	pos	.470	.339

Effect on Body Weight Development:

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MALES

Dose	wk -1	wk 74	diff.	% CON	wk 102	diff.	% CON
CON	29.4	48.1	18.8	-	45.5	16.1	-
0.3	29.4	48.3	18.9	100.6	46.3	16.9	104.6
2.0	29.4	41.7	12.3	65.7	39.0	9.6	59.7
10.0	29.1	38.7	9.6	51.1	38.8	9.8	60.6

FEMALES

Dose	wk -1	wk 74	diff.	% CON	wk 106	diff.	% CON
CON	24.1	38.9	14.8	-	37.6	13.5	-
0.3	26.0	40.6	14.6	98.6	39.3	13.3	98.5
2.0	24.4	33.0	8.6	58.1	32.9	8.5	63.0
8.0	24.6	31.5	6.9	46.6	32.0	7.4	54.8

MOUSE STUDY COMMENTS:

No evidence for a tumorigenic effect of pramipexole was found in either male or female mice.

A sufficient number of animals survived the study to adequately assess the long-term effects of the doses administered. The reduction in body weight gain, clinical signs (hyperactivity) and non-neoplastic lesions (fibro-osseous proliferation in femurs) evident at the intermediate and high test doses suggest that sufficiently high doses were used. However, the limited plasma exposure data suggests only a 13-fold difference between the highest exposures in mice and anticipated human exposure levels was achieved.

The marked impairment of body weight development precludes the use of higher doses, and interferes with the interpretation of the negative findings in this study from both the mid and high dose levels. The dose-response curve for reduction in weight gain in mice by pramipexole is very sharp; a dose as low as 0.5 mg/kg in the 13-week pilot study reduced weight gain by 17%. Thus, it seems unlikely that further evaluations of pramipexole tumorigenicity in mice using doses between the low and intermediate doses of this study would be useful.

RECOMMENDATIONS:

This study cannot be accepted as a valid assessment of the carcinogenic potential of pramipexole in mice because of the severe impairments of body weight gain at the intermediate and high dosage levels. Since similar problems with interpretation are likely to be encountered at doses between the low and intermediate doses of the present study, further evaluations of pramipexole tumorigenicity in this dosage range should not be required.

/S/

Thomas D. Steele, Ph.D.

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CC: NDA 20667
/Div. File, HFD-120
/GFitzgerald
/CAC
/TSteele

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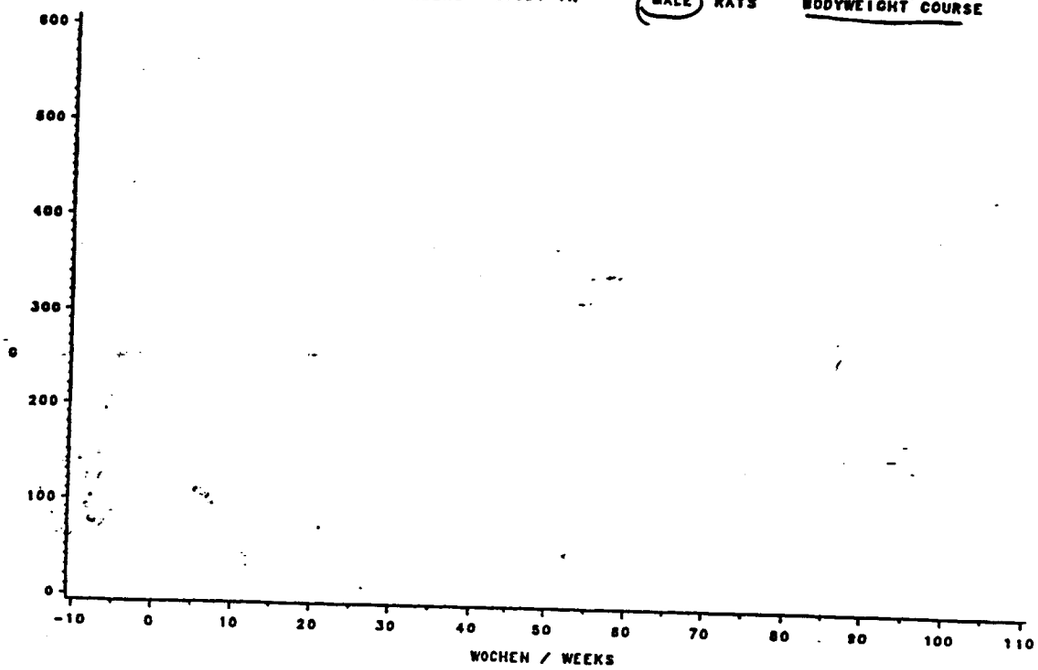
Fig. C.5.b.1.

SND 919 CL2Y
SND 919 CL2Y

675 P.O. 108 WOCHEN -VERSUCH MIT
P.O. 108 WEEKS -STUDY IN

MALE RATTEN
MALE RATS

KGW-VERLAUF
BODYWEIGHT COURSE



0:= KONTROLLE
CONTROL

1:= SND 919 CL2Y
0.3 MG/KG

2:= SND 919 CL2Y
2 MG/KG

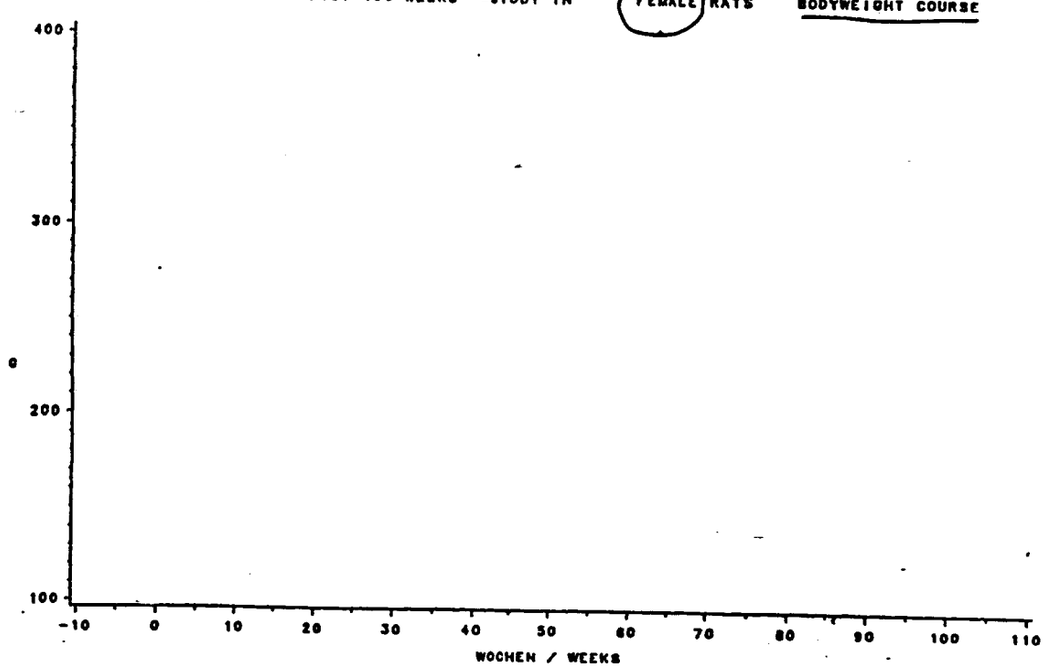
3:= SND 919 CL2Y
8 MG/KG

SND 919 CL2Y
SND 919 CL2Y

675 P.O. 108 WOCHEN -VERSUCH MIT
P.O. 108 WEEKS -STUDY IN

FEMALE RATTEN
FEMALE RATS

KGW-VERLAUF
BODYWEIGHT COURSE



0:= KONTROLLE
CONTROL

1:= SND 919 CL2Y
0.3 MG/KG

2:= SND 919 CL2Y
2 MG/KG

3:= SND 919 CL2Y
8 MG/KG

Distribution of Neoplasms in Rats

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

TR No. 7219-94-068

U94-0250

Name of company		
BOEHRINGER INGELHEIM KG	TABULATED STUDY REPORT	
Name of finished product	ref. to III.E.210	
Name of active ingredient: Pramipexole (SND 919 CL 2 Y)	4/9 Page Number	

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 <x> 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	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 TUMOUR	-	-	-	1	-	2	-	1	-	-
	LUTEOMA	-	-	-	4	-	-	-	1	-	-
	CARCINOMA, NOS	-	-	-	-	-	-	-	1	-	-
UTERUS	ADENOMA	-	-	-	1	-	-	-	-	-	-
	LEIOMYOMA	-	-	-	-	-	-	-	-	-	1
	HEMANGIOMA	-	-	-	-	-	-	-	2	-	1
	GRANULAR CELL TUMOUR	-	-	-	1	-	1	-	-	-	-
	ADENOCARCINOMA	-	2	-	2	-	2	-	2	-	1
	HEMANGIOSARCOMA	-	-	-	1	-	-	-	3	-	1

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

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

TR No. 7219-94-068

U94-0250

Name of company: BOEHRINGER INGELHEIM KG	TABULATED STUDY REPORT	
Name of finished product:	ref. to III.E.210	
Name of active ingredient: Pramipexole (SND 919 CL 2 Y)	6/9 Page Number	

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 <x> 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	m	f
Number of animals evaluated		50	50	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 f: **	-	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)

TR No. 7219-94-068

U94-0250

Name of company BOEHRINGER INGELHEIM KG Name of finished product Name of active ingredient Pramipexole (SND 919 CL 2 Y)	TABULATED STUDY REPORT ref. to III.E.210 8/9 Page Number	

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 <x> 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	m	f
Number of animals evaluated		50	50	50	50	50	50	50	50	50	50
Organ	Identification of the tumour										
ADIPOSE TISSUE	LIPOMA	1	-	2	1	-	-	1	-	-	-
EARS	HEMANGIOMA	-	-	-	-	1	-	-	-	-	-
TAIL	SCHWANNOMA	-	-	-	-	-	-	-	-	1	-

* P < 0.05 ** P < 0.01

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Test for Heterogeneity (Tab. C.5.b.8):

TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

ORGAN/TISSUE	TYPE OF NEOPLASM	SEX: MALE 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

TABLE FOR HETEROGENEITY ON NEOPLASTIC LESIONS

ORGAN/TISSUE	TYPE OF NEOPLASM	SEX: FEMALE 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

Mouse

Tab. C.5.a.6

TR No.: 7219-94-070

BOEHRINGER INGELHEIM KG Name of finished product	TABULATED STUDY REPORT ref. to III.E.210 2/6 Page Number	U93-0589
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: 28.06.93 Number: G70 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> 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	m	f
Number of animals evaluated								-			
Organ	Identification of the tumour										
BRAIN	OLIGODENDROGLIOMA	1	-	-	-	-	-	-	-	-	-
	NEOPLASM (NOS)	-	-	-	-	-	-	-	-	-	1
LUNGS	ADENOMA	22	9	11	8	12	13	8	6	13	6
	CARCINOMA	1	2	-	-	-	2	-	1	-	-
LIVER	ADENOMA/HEPATOC.	5	-	7	1	2	-	-	-	2	-
	HEMANGIOSARCOMA	3	1	4	-	2	1	1	-	1	-
	CARCINOMA/HEPATOC.	-	-	-	-	1	-	1	-	-	-
TONGUE	CARCINOMA/SQUAMOUS	1	-	-	-	-	-	-	-	-	-
DUODENUM	SARCOMA/OSSIFYING	-	-	-	-	-	-	1	-	-	-
TESTES	LEYDIG CELL TUMOR	4	-	3	-	2	-	-	-	5	-
PROSTATE	ADENOMA	1	-	-	-	-	-	-	-	-	-
SEMINAL											
VESICLES	LEIOMYOMA	1	-	-	-	-	-	-	-	-	-
OVARIES	LUTEOMA	-	-	-	-	-	-	-	-	-	1
	ADENOMA/TUBULAR	-	1	-	2	-	1	-	2	-	-
	TUMOR/GRANULOSA CELL	-	1	-	4	-	2	-	5	-	3
	LIPOMA	-	1	-	-	-	-	-	-	-	-

* P < 0.05 ** P < 0.01

25

BOEHRINGER INGELHEIM KG Name of finished product	TABULATED STUDY REPORT ref. to III.E.210	U93-0589
Name of active ingredient Pramipexole (SND 919 CL 2 Y)	4/6 Page Number	

ONCOGENIC/CARCINOGENIC POTENTIAL Tumour data

Ref. to document.: Volume: Page: to Addendum No.:
Report date: 28.06.93 Number: G70 Study period (years): 1989 - 1991

Number of tumours in all animals which were evaluated (without consideration of the causes and relevance) Biometrical evaluation yes <x> 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	m	f
Number of animals evaluated											
Organ	Identification of the tumour										
ADRENAL											
CORTEX	ADENOMA/A-CELL	-	-	-	-	1	-	-	-	-	1
	ADENOMA/B-CELL	6	-	3	-	3	-	6	-	3	1
	ADENOMA/B-CELL/EXTD.** (males)	8	-	5	-	3	-	2	-	-	-
	ADENOMA/Z. FASCICUL.	3	-	-	1	1	-	-	-	-	-
ADRENAL											
MEDULLA	MEDULL. TUMOR/BENIGN	1	-	-	-	-	-	-	-	-	-
	MEDULL. TUMOR/MALIGN.	-	-	-	1	-	-	-	-	-	-
MESENT.											
LYMPH NODE	HEMANGIOMA	-	-	-	1	-	-	-	-	-	-
SYSTEMIC											
NEOPLASMS	THYMIC LYMPHOMA* (females)	3	18	4	16	4	13	4	8	4	7
	NONSPECIF. LYMPHOMA	1	-	1	1	1	-	-	-	-	-
	NON-THYMIC LYMPHOMA	3	5	4	3	6	3	3	3	4	1
	MAST CELL TUMOR	1	-	-	-	-	-	2	-	-	1
	BONE MARROW LYMPHOMA	-	-	-	1	-	-	-	-	-	-
	HISTIOCYTIC SARCOMA	-	1	-	4	4	2	-	2	-	1
	MYELOID LEUKEMIA	-	1	-	-	-	-	-	-	-	-

* P < 0.05, ** P < 0.01 (=negative trend)

TR No.: 7219-94-070

Tab. C.5.a.7.

PATHOLOGY REPORT — PAGE : 781
STATISTICAL EVALUATION — BOE PROJECT: G 70

TEST ARTICLE : SND 919 CL 2 Y — PATHOL. NO.: 91009 HHW
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: K0 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#	-?? h... Con + Hi)
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#	-highest in con.
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-	0.1539	
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	

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

TR No.: 7219-94-070

Tab. C.5.a.7. (cont.)

PATHOLOGY REPORT
STATISTICAL EVALUATION

PAGE : 107/ 781
BOE PROJECT: G 70

TEST ARTICLE : SND 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR : BOEHRINGER INGELHEIM KG

PATHOL. NO.: 91009 HHW
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: 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

M+F
C = 9/100
LD = 3/100
MD = 6/100
HD = 4/100

Tab. C.5.a.7. (cont.)

PATHOLOGY REPORT

TEST ARTICLE : SND 919 CL 2 Y
TEST SYSTEM : MOUSE, 104 WEEKS, FEEDING
SPONSOR : BOEHRINGER INGELHEIM KG

PATHOL. NO.: 91009 HHW
DATE : 11-MAY-93
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

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

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

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

Sentences 2 and 3: The findings and significance of Leydig cell adenomas and hyperplasia in rats should be simplified since there is no experimental support for an effect of PPX on LH secretion or LH receptor number:

> "These findings are of questionable significance in humans because of their high background incidence in rats, the absence of similar changes in mice treated with PPX for 2 years, and the probable involvement of endocrine mechanisms that are not relevant to humans."

General: A statement that the results in mid- and high-dose female rats, and mid- and high-dose mice of both sexes are questionable or invalid due to the impairment of body weight gain needs to be included.

Statistical Review and Evaluation

OCT 24 1996

DATE:

NDA#: 20-667

APPLICANT: The Upjohn Company

NAME OF DRUG: Pramipexole Tablets

DOCUMENTS REVIEWED: Volumes 1.45, 1.49 Containing the Study Reports of the Mouse and Rat Studies and Volume 2.1 Dated Feb 13, 1996 Containing the Data Diskettes and Data Listings for these Studies.

APPEARS THIS WAY
ON ORIGINAL

I. Background

Dr. Thomas Steele (HFD-120) requested from the Division of Biometrics I a statistical review of the rat and mouse studies data as well as an evaluation of the sponsor's findings.

II. The Rat Study

II.a. Design

The product was studied for 107 weeks in male and female Chbb:THOM rats. There were two control groups and three treated groups of 50 animals/sex each. The compound was administered orally in the diet at 0.3, 2.0, and 8.0 mg/kg/day. The two control groups were combined in the analyses. Terminal sacrifice was performed during weeks 108 and 109.

II.b. Sponsor's Analyses of the Rat Study

Survival Analysis

The exact logrank test was used in concluding that time of death of the animals was not related to dose. Cummulative mortality was graphed for each sex.

Tumor Data Analysis

Tumor data with at least three tumor-bearing animals in any group were analyzed. The sponsor found an increased incidence in Leydig cell hyperplasia and adenomas in the male rats for the intermediate and high dose-groups. There were no statistically significant positive trends with dose in tumor incidence rates among the females. There were significant negative trends in pituitary adenomas (both sexes), neoplasms of the mammary gland in females, primary neoplasms in general, and benign adrenal medullary neoplasms in females. The sponsor concluded that the compound had no direct carcinogenic effect in rats. The observed significant changes (positive trend in Leydig cell hyperplasia/adenomas and negative trends in several tumor types) could be traced to functional effects of dopamine release.

II.c. Reviewer's Analyses

This reviewer independently performed analyses on the survival and the tumor data. For survival analysis the methods described in papers of Cox (Regression models and life tables, Journal of the Royal Statistical Society B 34, 187-220, 1972), and of Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika 52, 203-223, 1965) were used. The corresponding computer program was written by Thomas, Breslow, and Gart (Trend and homogeneity analyses of proportions and life table data, Computers and Biomedical Research 10, 373-381, 1977, Version 2.1). The tumor data were analyzed using the methods described in the

paper of Peto et al. (Guidelines for simple sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International Agency for Research against Cancer Monographs, Annex to Supplement, WHO, Geneva, 311-426, 1980) and the method of the exact permutation trend test developed by the Division of Biometrics. The following criteria for the levels of significance ensure a false positive rate of about ten percent for the trend tests of the usual two-species two-sexes studies: Tumors with less than 1.00% occurrence in the control group are considered rare and a positive trend test is statistically significant when it reaches a p-value of $\leq .025$ (one-sided). Higher tumor occurrences in the control group are considered common for these animals and a positive trend is statistically significant when its p-value is less than .005 (one-sided). An approximate permutation trend test is used when fatal and incidental tumors of the same kind are combined and have overlapping time intervals. All tests are survival adjusted and treatment groups are weighted by the actual dose levels.

Survival Analysis

Survival at Terminal Sacrifice ranged from percent (control - high dose) among the male rats and from 77 to 60 percent (control - low dose) among the female rats as can be seen in the Table 1. The life table analysis of the male mortality data showed no significant linear Cox trend statistic or generalized Kruskal/Wallis analysis, nor were any pairwise comparisons between treated and untreated groups significant. The life table analysis of the female mortality data showed a similar pattern of no statistically significant relationship of dose with mortality (Table 2 Figures 1 and 2).

There are some minor numeric differences between the number of animals being terminally sacrificed. It appears that the sponsor treated animals dying naturally during the weeks of terminal sacrifice as natural death whereas this reviewer treated them as terminally sacrificed. No difference in conclusion results from these slightly different approaches. Should an animal which died naturally during weeks 108 and 109 exhibit a fatal tumor, it would be properly handled as such by this reviewer as well.

Tumor Data Analysis

This reviewer constructed tumor incidence tables for each recorded tissue for any tumor, treating fatal, incidental, and undetermined separately. Possible positive tumor trends with dose were then statistically analyzed adjusting for mortality despite the overall nonsignificant difference in survival. Leydig cell adenomas in the male rats were common in all animals but showed such an increase in incidence with dose. The observed trend in incidental tumors resulted in a p-value of .0233; the undetermined tumors had a p-value of .0664. There were no fatal Leydig cell adenomas. Combining all tumor occurrences gave an overall trend statistic with p=.0065. However, as these tumors occurred also frequently among the control animals, this level is not considered sufficient (higher than p=.005) to be called statistically significant. At the request of the pharmacologist, the pairwise comparisons with each of the control groups and their

combination are given in Appendix 1. As these are only pairwise comparisons, the appropriate criteria for statistical significance are p=.05 for rare tumors and p=.01 for common tumors. Using the p=.01 for common tumors, it can be seen that comparisons with the second control group or with the combined control groups reach statistical significance for Leydig Cell adenomas coded as incidental or for all Leydig Cell adenomas. Comparisons with the first control group do not reach statistical significance, nor do any based on Leydig Cell adenomas coded as undetermined and analyzed as if they were incidental tumors.

Among the female rats, none of the possible positive trends reached the statistical criteria of significance.

This reviewer did not analyze any negative trends observed in the tumor occurrences. However, as the sponsor mentioned, some of these were very striking.

II.d. Validity of the Rat Study

Before concluding that the rat study (both for males and females) showed no tumorigenic effect of pramipexole, the validity of the study needs to be determined. For this, two questions need to be answered (Haseman, Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984):

(i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?

(ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following are some rules of thumb as suggested by experts in the field: Haseman (Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol 5, pp 66-78, 1985) had found that on the average, approximately 50 % of the animals in the high dose group survived the two-year study. In a personal communication with Dr. Karl Lin of HFD-715, he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered as a sufficient number and adequate exposure. Chu, Cueto, and Ward (Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981) proposed that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50 % survival at one year". From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

(i) "A dose is considered adequate if there is a detectable weight loss of up to 10 % in a

dosed group relative to the controls."

(ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

(iii) "In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls."

In another paper, Bart, Chu, and Tarone (Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, 957-974, 1979), stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, "Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is a indication that the treatment has been tested on levels at or approaching the MTD."

The lowest survival of the animals at two years was 60 percent. Therefore, it is obvious that there were a sufficient number of animals throughout the study to manifest any late developing tumors.

From the attached Figures 3 and 4, the sponsor's group mean body weight plots, one can see that the dosed animals experienced lower body weight than the controls. As given in the Tables below, at week 74 and at the end of the study, the medium and high dosed male rats experienced lower weight gain of up to 9 percent relative to that of their controls. For the female rats these differences were much more pronounced showing a 28 percent difference in weight gain of the controls versus the high dosed animals at the end of the study. Therefore, for the male rats, the findings would support the high dose being close to the MTD, whereas for the female rats one has to be concerned whether their lack of tumor incidences may be due, at least in part, to the fact that leaner animals develop less tumors, and that the carcinogenic potential of this compound cannot be assessed in this sex and species.

AVERAGE WEIGHT: MALE RATS

Dose	Wk: -1	Wk: 74	Diff.	% of C	Wk: 106	Diff.	% of C
C	145.897	585.375	439.478		588.082	442.185	
L	144.291	557.190	412.899	94.0	581.718	437.427	98.9
M	144.536	544.794	400.258	91.1	553.860	409.324	92.6
H	143.463	548.605	405.142	92.2	562.662	419.199	94.8

AVERAGE WEIGHT: FEMALE RATS

Dose	Wk: -1	Wk: 74	Diff.	% of C	Wk: 106	Diff.	% of C
C	132.379	305.833	173.454		315.891	183.512	
L	131.878	293.743	161.865	93.3	302.585	170.707	93.0
M	131.096	271.263	140.167	80.8	275.823	144.727	78.9
H	130.354	264.281	133.927	77.2	261.888	131.534	71.7

A numerically increasing mortality trend with dose, though not significantly so, is also a measure of assessing whether the high dose was close to the MTD. For the present data, neither the male nor the female mortality data showed any ordering with dose.

In summary, the data show that both the male and the female rats lived long enough to show any late-developing tumors. However, assessing whether the high dose was close to the MTD proved more difficult. The sponsor documented the reasons for chosing 8 mg/kg as the high dose, namely because it fell into the lower third of the toxic dose range. The application of the criteria put forth by experts to assess the high dose as being close to the MTD give inconclusive results. There was weight reduction in the dosed animals, but far beyond 10 percent for the female rats. Mortality did not show any association with dose. Trends in non-neoplastic findings may help the pharmacologist in the determination of the validity of this study.

III.The Mouse Study

III.a. Design

This study was conducted in Chbb:NMRI mice for two years. For each sex there were 50 animals per group. The two control groups were combined in the analyses. The dosed animals received 0.3, 2.0, and 10.0 mg/kg/day in the diet. Terminal sacrifice was performed during weeks 105 and 106 on all surviving animals.

III.b. Sponsor's Analyses of the Mouse Study

Survival Analysis

The sponsor used the exact logrank test for group comparisons of the mortality data and provided graphs of cummulative mortality. They stated that the rate of premature decedents was higher in

the treated animals than in the controls, significantly so among the male mice. The male mice also exhibited a significant level of heterogeneity.

Tumor Data Analysis

Tumor incidence rates were analyzed according to their context of observation. No statistically significant positive trends in tumor incidence rates with dose were observed for any neoplastic lesions. The sponsor discussed the significant increased incidence and severity of fibro-osseous proliferative lesions in the femurs of treated females and several (some significant) negative trends in a variety of tumors. These were attributed to the pharmacological actions of the product.

III.c. Reviewer's Analyses

The same statistical methods and approaches discussed for the rat study were applied to the mouse data.

Survival Analysis

The generallized Kruskal/Wallis test showed a significant trend with dose and signifcant heterogeneity for the male mortality data (p=.040 for trend and p=.017 for heterogeneity). The adjusted Cox test for trend did not reach significance for trend (p=.067), but also exhibited significant heterogeneity (p=.016). These findings were supported by significant pairwise comparisons of the dosed groups with the controls. No differences were observed between the mortality experiences of the dosed animals. The lifetable analysis of the female mice data showed no statistically significant trend with dose, nor any significant departure from linearity (Tables 3 and 4, Figures 5 and 6).

The intercurrent mortality tables of the sponsor and this reviewer differ slightly because this reviewer counted animals dying naturally during the time of terminal sacrifice as part of the sacrificed animals, whereas the sponsor treated them as natural deaths. No difference in conclusions results from this discrepancy.

Tumor Data Analysis

None of the tumor findings exhibited a possible positive trend with dose.

There was, however, one minor point of confusion: the sponsor called all tumor findings 'incidental' which in this Division is interpreted to mean that they did not cause the death of an animal. There are, however, some tumors recorded as fatal. The precise meaning in the sponsor's submission is not clear to this reviewer, but was taken to be of no importance.

III.d. Validity of the Mouse Study

Before concluding that the mouse study showed no tumorigenic effect of pramipexol, the validity of the study needs to be determined. The same criteria used in the assessment of the validity of the rat study will be applied to the mouse data.

The survival of the mice after two years of treatment was at least 56 percent, demonstrating that there were a sufficient number of animals available in any dose group to exhibit late developing tumors if the compound causes them.

Figures 7 and 8 are reproductions of the sponsor's average weights over the course of the study. It is clear that the medium and high dose animals experienced an early and sustained reduction in weight gain. The differences between the average weights of the high dose and the controls reach about 19 percent for both the male and female mice. The differences in weight gain are even more striking, with 49 and 53 percent at week 74, and 39 and 45 percent at week 102 for the male and female high dose mice respectively. These findings do not support a conclusion that the high dose was close to the MTD, but raise concerns whether these leaner animals exhibited fewer tumors because of their condition rather than because the compound was non-carcinogenic. The differences in weight gain between the medium dose animals and the controls were similar to those of the high dose animals and would not support the medium dose being close to the MTD on this measure.

AVERAGE WEIGHT: MALE MICE

Group	Wk: -1	Wk: 74	Diff.	% of C	Wk: 102	Diff.	% of C
C	29.386	48.127	18.841		45.503	16.117	
L	29.437	48.294	18.857	100.62	46.296	16.859	104.60
M	29.361	41.678	12.317	65.72	38.990	9.629	59.74
H	29.056	38.679	9.623	51.35	38.822	9.766	60.59

AVERAGE WEIGHT: FEMALE MICE

Group	Wk: -1	Wk: 74	Diff.	% of C	Wk: 102	Diff.	% of C
C	24.144	38.932	14.788		37.628	13.484	
L	25.952	40.609	15.557	105.20	39.291	14.239	105.60
M	24.378	32.983	8.605	58.19	32.890	8.492	62.98
H	24.568	31.469	6.901	46.67	32.028	7.460	55.32

There was a trend in mortality with dose for the male mice but not for the female mice. For the females there was a somewhat higher mortality in the dosed animals than in their controls, but there was no direction in these with increasing dose. The pharmacologist may want to evaluate possible dose relationships in clinical signs and histopathological effects in his conclusion whether the study was conducted in such a way that tumors could have been detected if the compound causes them. From the statistical point of view, one cannot conclude that the compound is a non-carcinogen.

IV. Summary and Conclusion

The two year rat study seemed to be a well executed study in which the doses administered had no apparent effect on survival. The only possibly significant linear trend in tumor incidence rates with dose was Leydig cell adenomas in the male rats. The associated p-value was .0065, which, according to this Division's criteria to control for false positive findings, is not considered a statistically significant finding. Some of the pairwise comparisons of the high and mid doses with control group 2 or the combined controls did reach statistical significance when a level of significance appropriate for pairwise comparisons was used. Other pairwise comparisons did not meet this criterion. In the subsequent evaluation of the validity of this study, this reviewer found that there were sufficient numbers of animals surviving till final sacrifice to exhibit any late developing tumors. For the male animals one could conclude the high dose was close to the MTD by demonstrating that the differential in weight gain of the dosed animals with respect to their controls was not more than 10 percent. However, no ordering of survival with dose was found. For the female rats, the weight gain was suppressed by up to 28 percent, far exceeding the 10 percent criterion. Therefore, from a statistical point of view it cannot be concluded that the product is a non-carcinogen. The evalutaion of clinical signs and of gross histopathological effects for dose relationships may help the pharmacologist in assessing the validity of this study.

The two year mouse study also appeared to be a well conducted experiment. The survival experience of the male mice was reduced with dose, significantly so by at least one statistical test. The associated significant heterogeneity points to the fact that the dosed animals experienced higher mortality but not in strict order with dose. The female mice showed no difference in mortality across groups. Neither the male nor the female mice exhibited any increase in tumor incidence rates with dose. In the evaluation of the study's validity it was found that there were sufficient numbers of animals living till the end of the study to exhibit any late developing tumors should the compound cause them. However, the mid and high dose animals gained substantially less weight than their controls. At the end of the study, the high dose females had gained only 55 percent of the weight their controls had gained and the males had gained only 61 percent of what their controls had gained. This clearly begs the question whether this large differential in weight gain could mask a tumorigenic potential of the compound if leaner animals develop fewer tumors.

A final point is, that the sponsor's statistical methods applied to the mortality data and to the tumor data were not clearly described and their results not presented. Therefore, a complete statistical review had to be performed.

/S/

Roswitha E. Kelly
Mathematical Statistician

APPEARS THIS WAY
ON ORIGINAL

Concur:

/S/

Todd Sahlroot, Ph. D.
Acting Team Leader

/S/

George Chi, Ph.D.
Director, DB I

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY

cc:Archival NDA 20-667, Pramipexole Tablets, The Upjohn Company
HFD-120/Division File
HFD-120/Dr. Steele
HFD-120/Dr. Fitzgerald
HFD-710/Chron.
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Ms. Kelly
HFD-710/RKELLY/10/15/96/wp-pramipex.rev

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ON ORIGINAL

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ON ORIGINAL

Table 1
INTERCURRENT MORTALITY RATES

MALE RATS

Weeks	0	0.3	mg/kg/day 2.0	8.0
0- 52	2/99 (2%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
53- 78	1/97 (3%)	0/50 (0%)	2/49 (6%)	1/49 (4%)
79- 92	6/96 (9%)	2/50 (4%)	1/47 (8%)	2/48 (8%)
93-107	8/90 (17%)	5/48 (14%)	2/46 (12%)	6/46 (20%)
Term. Sac.	82/99 (83%)	43/50 (86%)	44/50 (88%)	40/50 (80%)

FEMALE RATS

Weeks	0	0.3	mg/kg/day 2.0	8.0
0- 52	3/100 (3%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
53- 78	7/97 (10%)	2/49 (6%)	0/50 (0%)	3/49 (8%)
79- 92	5/90 (15%)	5/47 (16%)	7/50 (14%)	1/46 (10%)
93-107	8/85 (23%)	12/42 (40%)	7/43 (28%)	6/45 (22%)
Term. Sac.	77/100 (77%)	30/50 (60%)	36/50 (72%)	39/50 (78%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

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Table 2

Results of Intercurrent Mortality Analyses

Male Rats

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C,L,M,H	pos	.500	.484
C,L	neg	.748	.567
C,M	neg	.592	.489
C,H	pos	.821	.660
L,M	neg	.824	.881
L,H	pos	.541	.364
M,H	pos	.427	.317

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Female Rats

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C,L,M,H	neg	.397	.385
C,L	pos	.083	.105
C,M	pos	.743	.715
C,H	neg	.972	.773
L,M	neg	.348	.349
L,H	neg	.097	.083
M,H	neg	.643	.518

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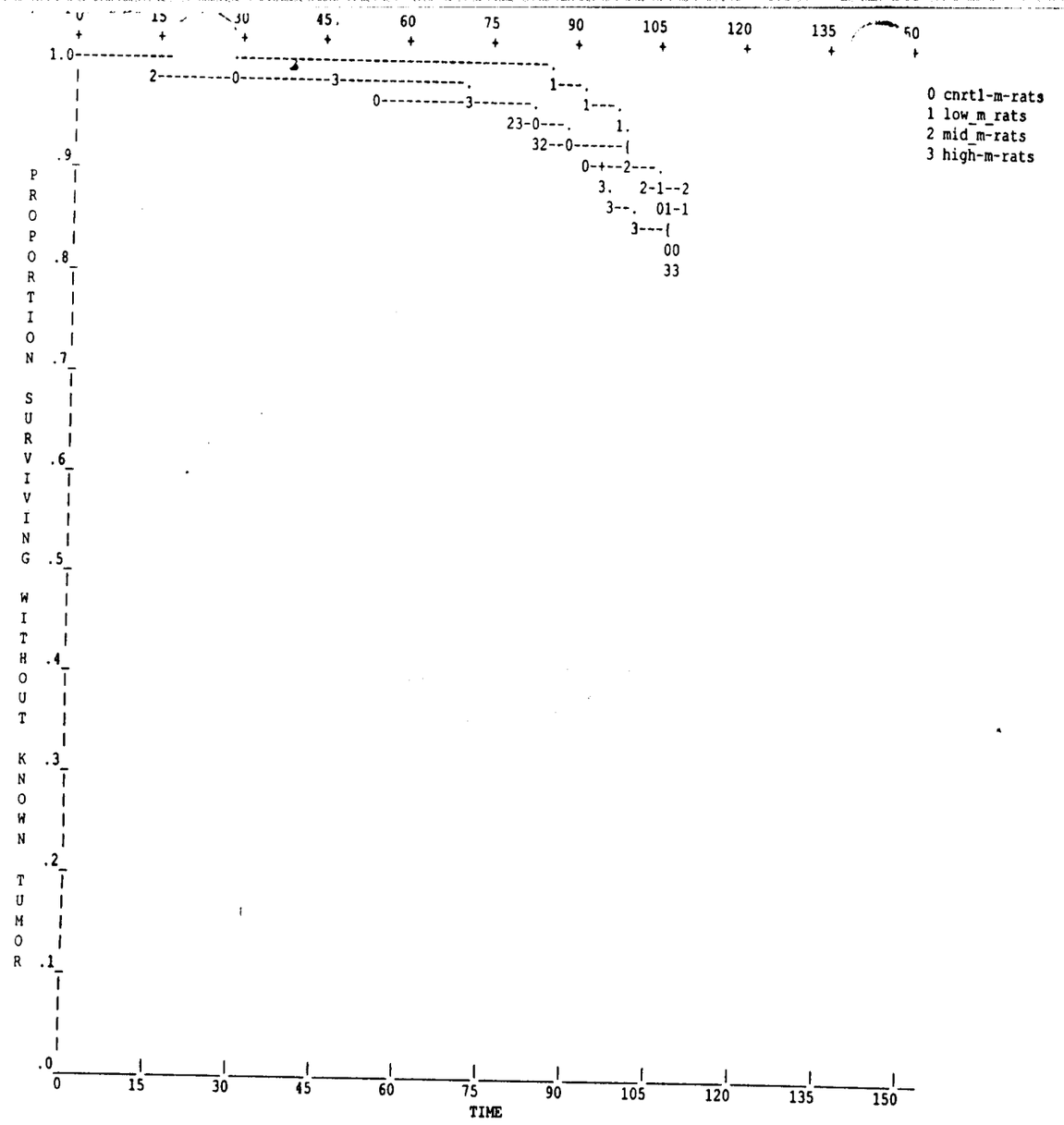
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1 low_m_rats
2 mid_m-rats
3 high-m-rats
PROPORTION SURVIVING WITHOUT KNOWN TUMOR
1.0
.9
.8
.7
.6
.5
.4
.3
.2
.1
.0
0
15
30
45
60
75
90
105
120
135
150
TIME

Figure 1

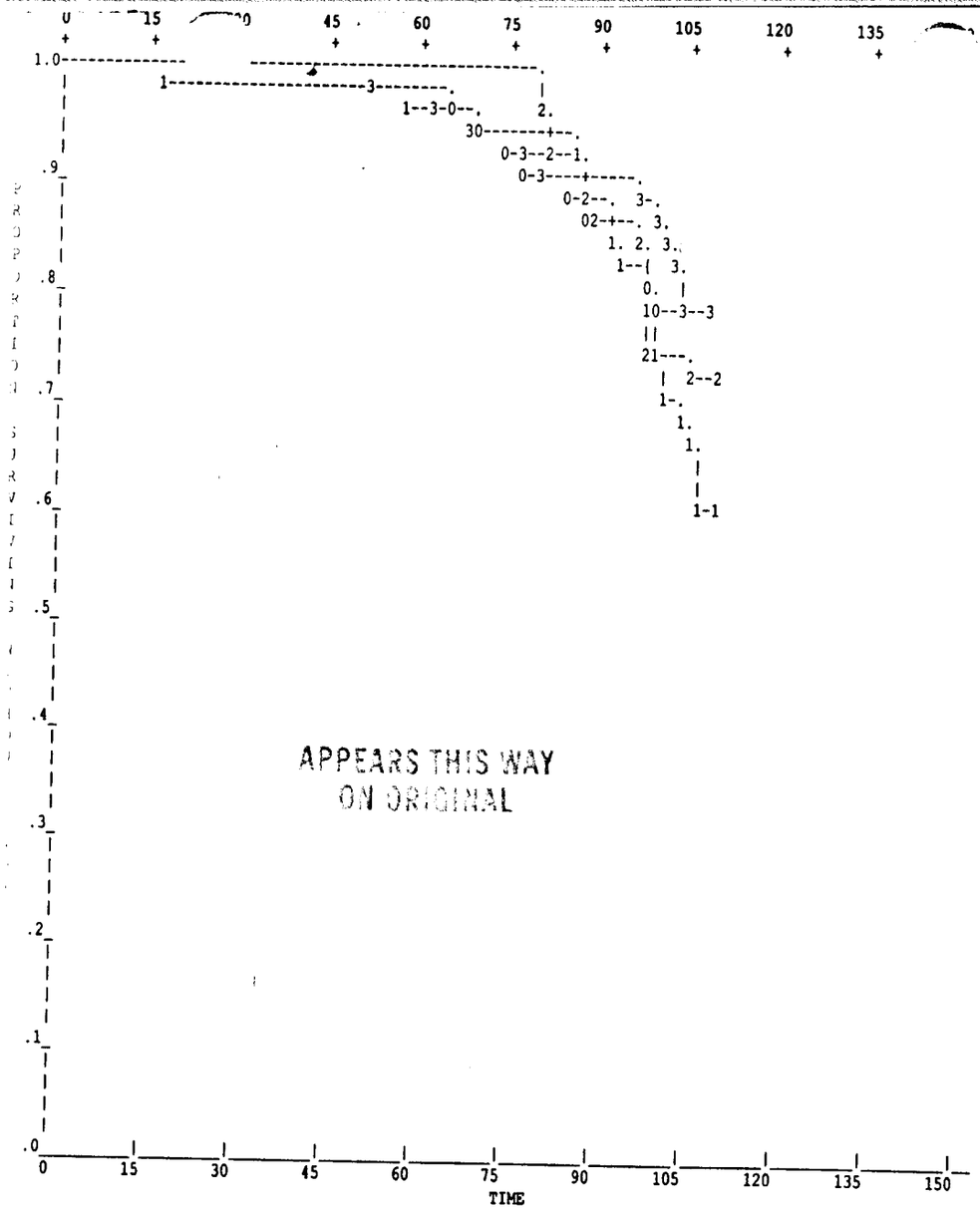

Figure 2

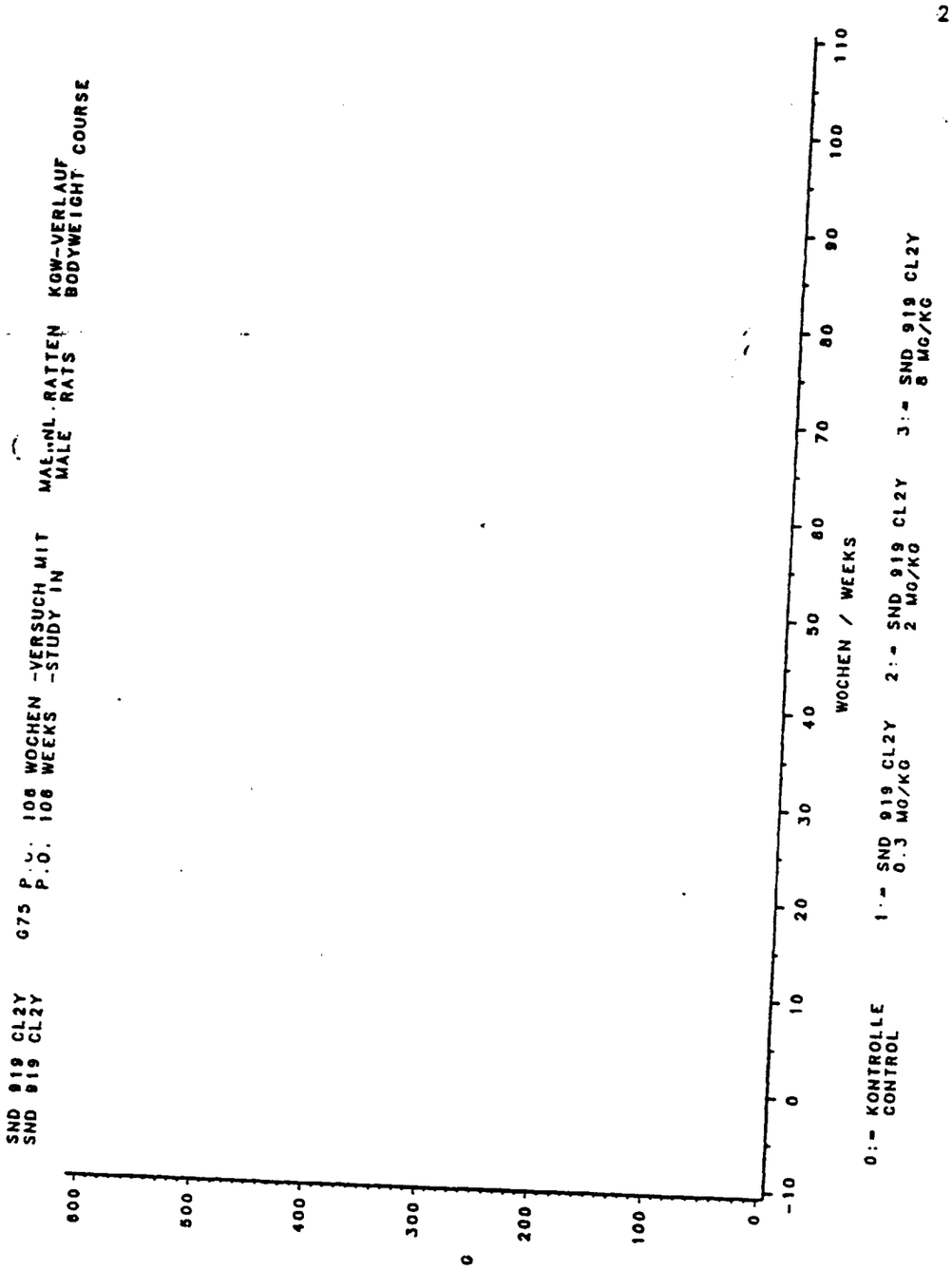
SND 919 CL2Y
SND 919 CL2Y
675 P.O. 108 WOCHEN -VERSUCH MIT
P.O. 108 WEEKS -STUDY IN
MAE.NL. RATTEN KGW-VERLAUF
MALE RATS BODYWEIGHT COURSE
600
500
400
300
200
100
0
-10
0
10
20
30
40
50
60
70
80
90
100
110
WOCHEN / WEEKS
0:= KONTROLLE
CONTROL
1:= SND 919 CL2Y
0.3 MG/KG
2:= SND 919 CL2Y
2 MG/KG
3:= SND 919 CL2Y
8 MG/KG

Figure 3

TR No. 7219-94-068

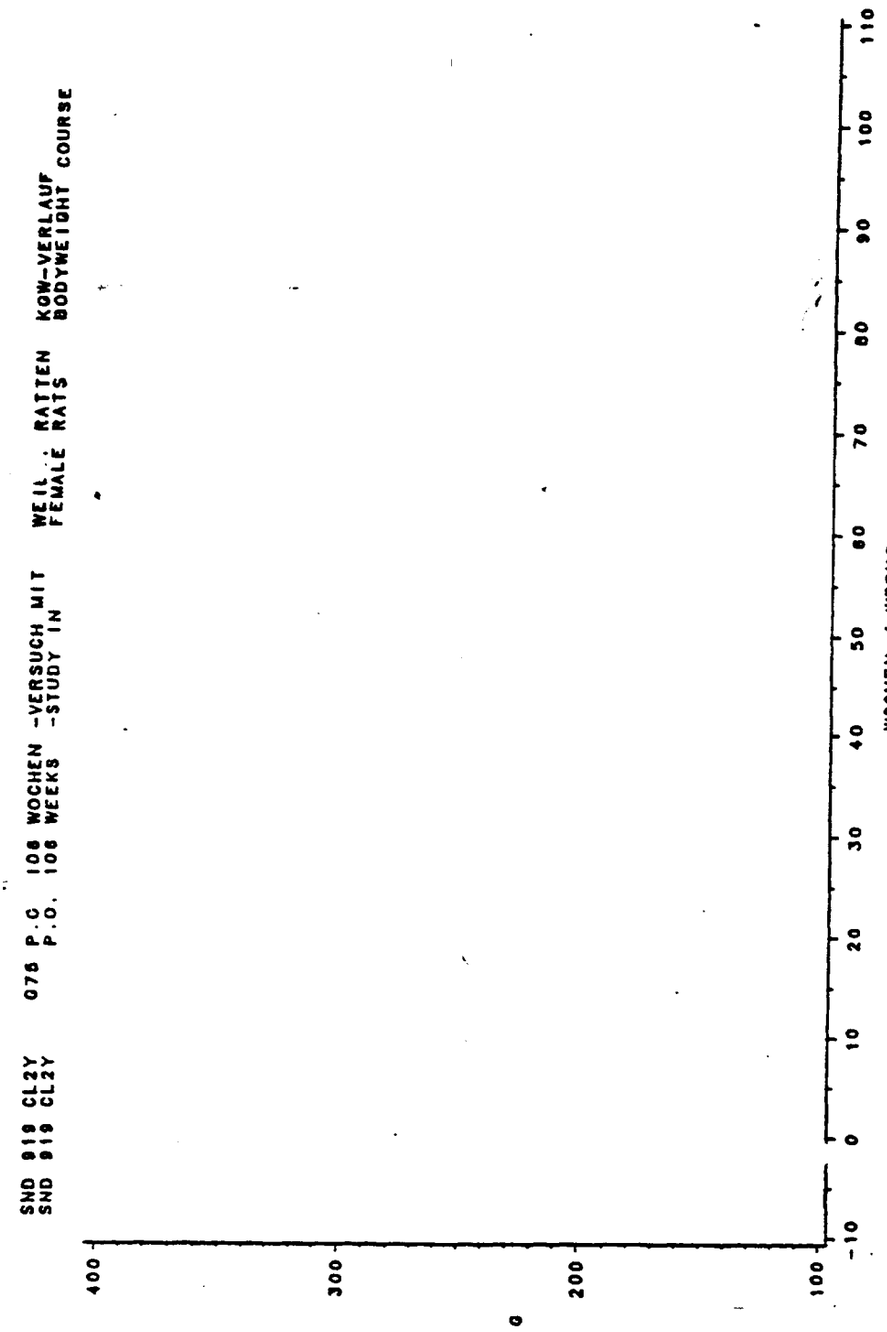

Figure 4

Table 3
INTERCURRENT MORTALITY RATES

MALE MICE

Weeks	0	0.3	mg/kg/day 2.0	10.0
0- 52	1/100 (1%)	3/50 (6%)	6/50 (12%)	4/50 (8%)
53- 78	8/99 (9%)	2/47 (10%)	5/44 (22%)	9/46 (26%)
79- 92	7/91 (16%)	11/45 (32%)	7/39 (36%)	4/37 (34%)
93-104	5/84 (21%)	5/34 (42%)	3/32 (42%)	3/33 (40%)
Term. Sac.	79/100 (79%)	29/50 (58%)	29/50 (58%)	30/50 (60%)

FEMALE MICE

Weeks	0	0.3	mg/kg/day 2.0	10.0
0- 52	0/100 (0%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
53- 78	5/100 (5%)	5/49 (12%)	2/48 (8%)	3/46 (14%)
79- 92	12/95 (17%)	8/44 (28%)	4/46 (16%)	8/43 (30%)
93-104	16/83 (33%)	8/36 (44%)	10/42 (36%)	7/35 (44%)
Term. Sac.	67/100 (67%)	28/50 (56%)	32/50 (64%)	28/50 (56%)

Note: Except for Terminal Sacrifice, an entry of this table represents the number of animals dying or being sacrificed during the time interval divided by the number of animals entering the time interval. The entry in parenthesis is the cumulative mortality percent, i.e. the cumulative percent of animals dying up to the end of the time interval. The entry for Terminal Sacrifice represents the number of animals surviving till the end of the study divided by the initial number of animals. The entry in parentheses for this row represents the number of animals surviving to terminal sacrifice.

Table 4

Results of Intercurrent Mortality Analyses

Male Mice

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C,L,M,H	pos	.067	.040*
C,L	pos	.012*	.011*
C,M	pos	.006**	.002**
C,H	pos	.011*	.005**
L,M	pos	.857	.507
L,H	neg	.882	.625
M,H	nrg	.982	.873

Female Mice

Groups Compared	Direction	Two-tailed P-Value of Test	
		Cox	Kruskal/Wallis
C,L,M,H	pos	.253	.205
C,L	pos	.153	.077
C,M	pos	.768	.607
C,H	pos	.163	.084
L,M	neg	.445	.314
L,H	pos	.984	.999
M,H	pos	.470	.339

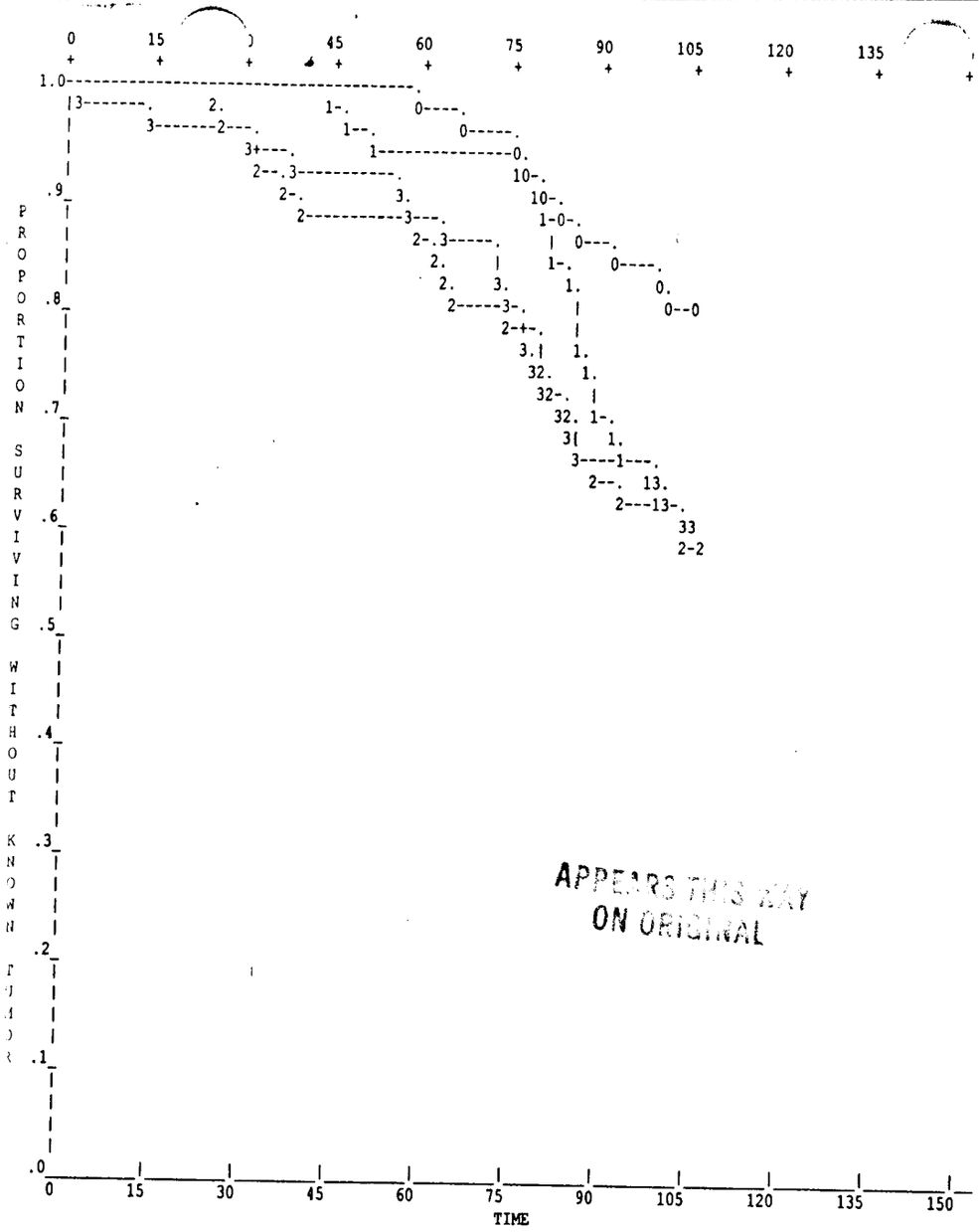

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Figure 5

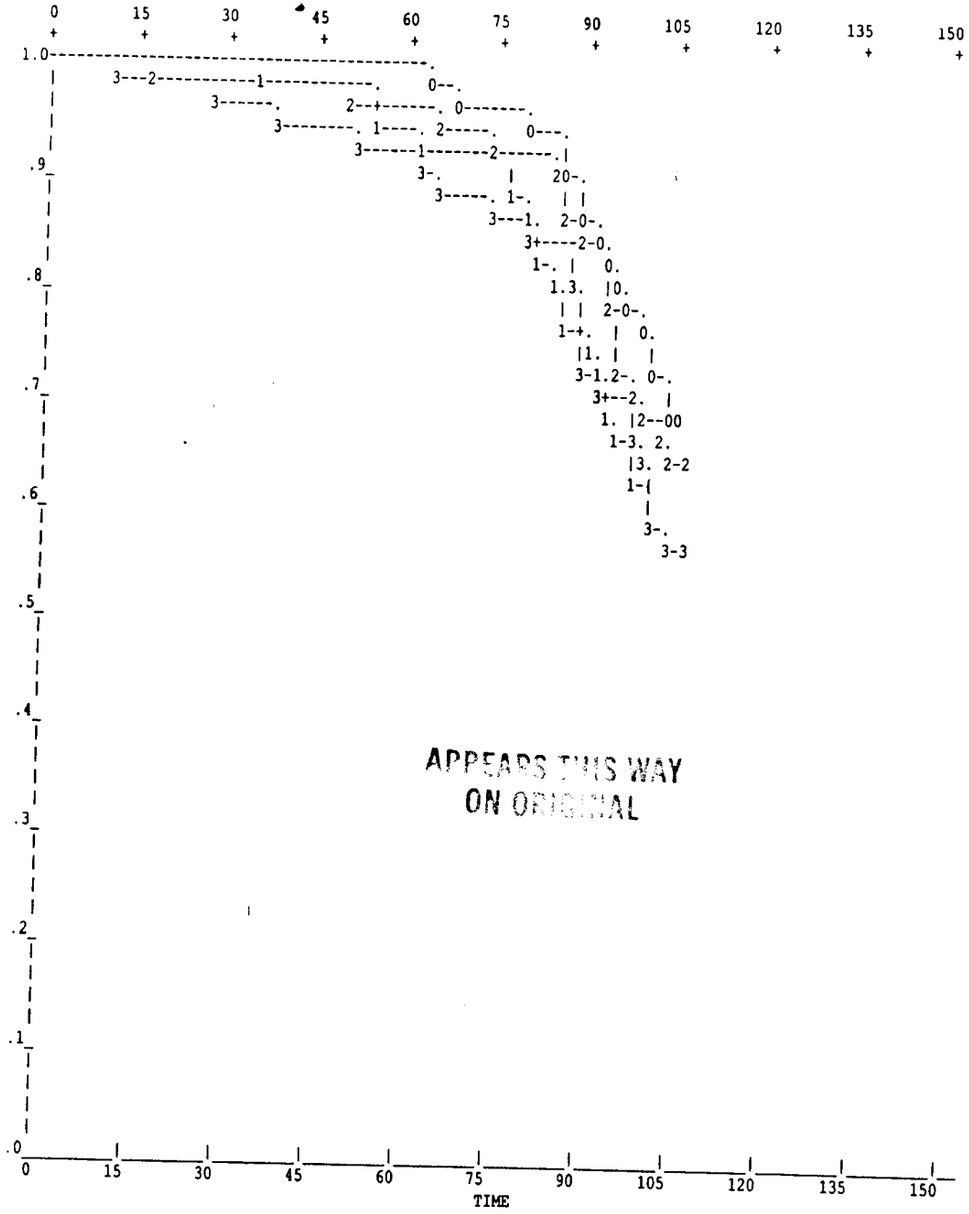

Figure 6

SND 919 CL2Y
SND 919 CL2Y
670 P.O. 104 WOCHEN -VERSUCH MIT
P.O. 104 WEEKS -STUDY IN
MAEUSEN MAUSE
MALE MICE
KGW-VERLAUF
BODYWEIGHT COURSE
G
60
50
40
30
20
-11
-1
10
20
30
40
50
60
70
80
90
100
110
WOCHEN / WEEKS
0:= KONTROLLE
CONTROL
1:= SND 919 CL2Y
0.3 MG/KG
2:= SND 919 CL2Y
2 MG/KG
3:= SND 919 CL2Y
10 MG/KG

Figure 7

TR No.: 7219-94-070

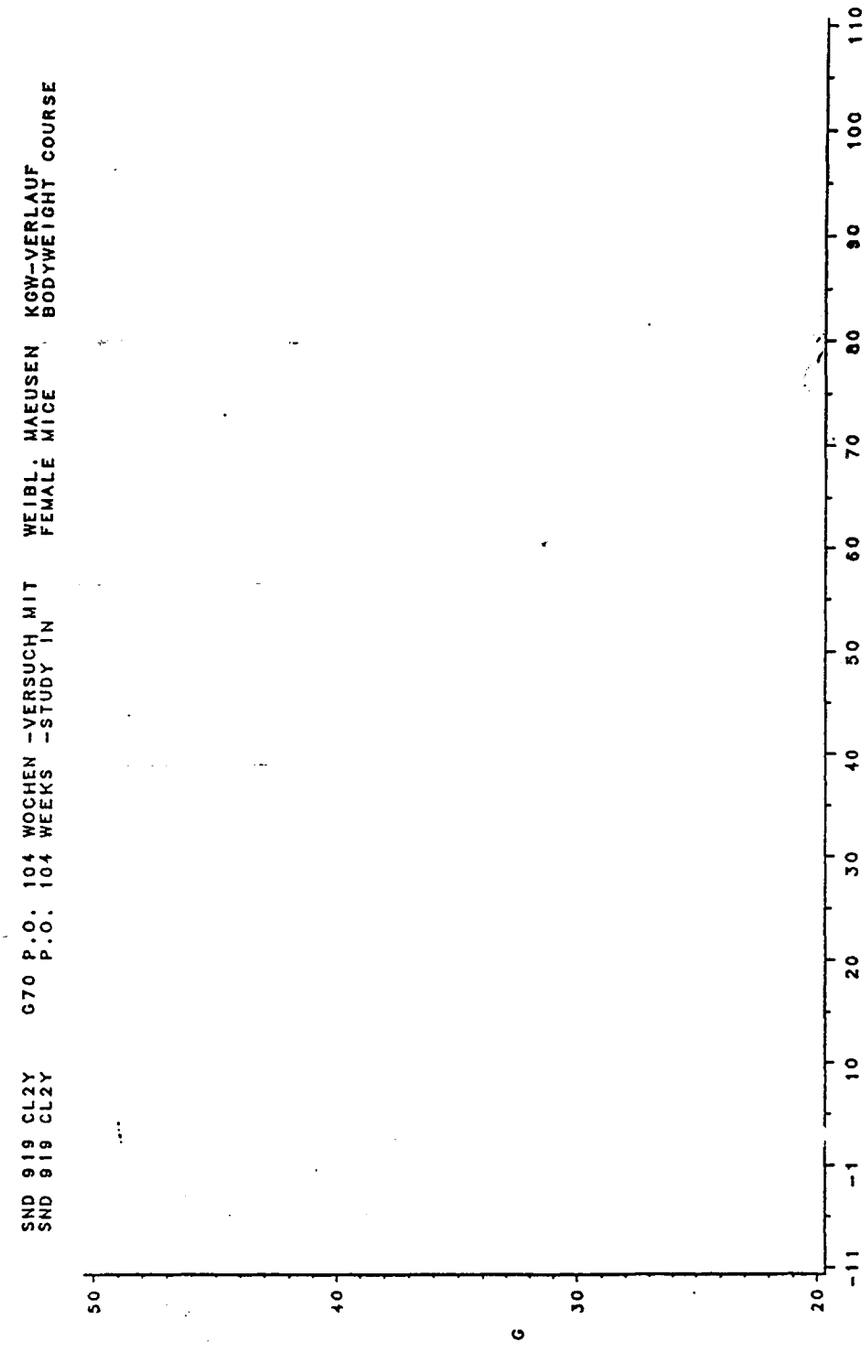

Figure 8

APPENDIX 1

P-VALUES ASSOCIATED WITH PAIRWISE COMPARISONS

Leydig Cell Adenomas Coded as Incidental:

Comparison	Associated p
Control 1 vs. High	.0604
Control 1 vs. Mid	.0322
Control 2 vs. High	.0075
Control 2 vs. Mid	.0031
Combined Crls vs. High	.0087
Combined Crls vs. Mid	.0029

Leydig Cell Adenomas Coded as Undetermined:

Comparison	Associated p
Control 1 vs. High	.6000
Control 1 vs. Mid	.5333
Control 2 vs. High	.4371
Control 2 vs. Mid	.5833
Combined Crls vs. High	.3764
Combined Crls vs. Mid	.7143

All Leydig Cell Adenomas:

Comparison	Associated p
Control 1 vs. High	.0620
Control 1 vs. Mid	.0610
Control 2 vs. High	.0067
Control 2 vs. Mid	.0028
Combined Crls vs. High	.0072
Combined Crls vs. Mid	.0040