Table 2: Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	2.89	0.0890
	Depart from Trend	6.77	0.0338
	Homogeneity	9.66	0.0216
Kruskal-Wallis	Dose-Mortality Trend	3.38	0.0661
	Depart from Trend	6.21	0.0447
	Homogeneity	9.59	0.0224

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Source: C:\DATA\KEPRA\rat.dat

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ON ORIGINAL

Table 3: PAIRWISE COMPARISONS BETWEEN COMBINED CONTROLS AND HIGH DOSE MALE RATS

Sorted by Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
AC	Abdominal cavity	33	lipochondroma	1.0000	0.7844	0.7846
AD	Adrenals	58	phaeochromocytoma - benig	0.8841	0.7495	0.7496
AD	Adrenals	59	phaeochromocytoma - malig	1.0000	0.9622	0.9623
BO	Bone	54	osteosarcoma	1.0000	0.7752	0.7753
BN	Brain	53	oligodendroglioma	0.3504	0.0866	0.0867
BN	Brain	23	granular cell meningioma	0.3933	0.1071	0.1072
BN	Brain	25	haemangiosarcoma	0.4086	0.1145	0.1146
BN	Brain	5	astrocytoma	1.0000	0.7781	0.7783
BN	Brain	51	mixed glioma	1.0000	0.8603	0.8603
KD	Kidneys	60	renal adenoma	0.3933	0.1071	0.1072
KD	Kidneys	61	renal carcinoma	0.3933	0.1071	0.1072
KD	Kidneys	25	haemangiosarcoma	0.4086	0.1145	0.1146
LI	Liver	38	liver cell tumour - malig	0.6346	0.3780	0.3781
LNI	Lymph nodes Inguinal	24	haemangioma	1.0000	0.7324	0.7326
LNM	Lymph nodes Mesenteric	24	haemangioma	1.0000	0.7407	0.7409
LY	Lymphoid/multicentric tum	26	histiocytic sarcoma	0.6266	0.4619	0.4620
LY	Lymphoid/multicentric tum	41	malignant lymphoma	1.0000	0.7679	0.7681
	Lymphoid/multicentric tum	52	myeloid leukaemia	1.0000	0.8504	0.8505
	Mammary Glands	44	mammary adenocarcinoma	1.0000	0.6342	0.6345
MG	Mammary Glands	47	mammary fibroadenoma	1.0000	0.8758	0.8759
PL	Palate	67	squamous cell carcinoma w	1.0000	0.7781	0.7783
PA	Pancreas	28	islet cell adenoma	0.9721	0.9153	0.9154
PA	Pancreas	17	exocrine adenoma	1.0000	0.7836	0.7838
PA	Pancreas	29	islet cell carcinoma	1.0000	0.7896	0.7898
PI	Pituitary	2	adenoma	0.9880	0.9779	0.9779
PI	Pituitary	11	carcinoma	1.0000	0.7686	0.7688
SM	Sketetal Muscle	18	fibroma	0.2778	0.0534	0.0535
SK	Skin	63	sebaceous adenoma	0.1519	0.0386	0.0387
SK	Skin	9	basosquamous cell carcino	0.3933	0.1071	0.1072
SK	Skin	31	keratoacanthoma with ulce	0.3933	0.1071	0.1072
SK	Skin	68	squamous cell papilloma	0.6244	0.3715	0.3717
SK	Skin	15	dermal fibroma	0.6346	0.3780	0.3781
SK	Skin	30	keratoacanthoma	0.8862	0.7937	0.7937
SK	Skin	18	fibroma	1.0000	0.8739	0.8740
ST	Stomach	69	squamous cell papilloma -	1.0000	0.8739	0.8740
SU	Subcutis	20	fibrosarcoma	0.6085	0.3565	0.3566
SU	Subcutis	34	lipoma	0.9238	0.8174	0.8175
SU	Subcutis	18	fibroma	0.9810	0.9374	0.9374
SU	Subcutis	19	fibroma with ulcer	1.0000	0.7896	0.7898
SU	Subcutis	35	lipoma with fibrosis	1.0000	0.7896	0.7898
	Tail	15	dermal fibroma	1.0000	0.7896	0.7898
TL	Tail	30	keratoacanthoma	1.0000	0.7836	0.7838
TE	Testes	27	interstitial cell tumour	0.7592	0.6419	0.6420
TY	Thymus	39	lymphocytic thymoma	1.0000	0.7881	0.7883
TH	Thyroids	57	parafollicular cell carci	0.5011	0.3920	0.3921

Table 3: con'd

TH	Thyroids	56	parafollicular cell adeno	0.6346	0.3780	0.3781
TH	Thyroids	21	follicular adenoma	1.0000	0.7896	0.7898

Table 4: Number of Animals
Species: Rat
Sex: Female

Week	Treatment Group CTRL N	LOW N	MED N	HIGH N	Total N
0-52	2		.		2
53-78	8		3		26
79-91	20		4		34
92-104	24		7		53
105-107	46		36		135
Total	100		50		250

Source: C:\DATA\KEPRA\rat.dat

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ON ORIGINAL

Table 5: Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.35	0.2458
	Depart from Trend	8.52	0.0141
	Homogeneity	9.87	0.0197
Kruskal-Wallis	Dose-Mortality Trend	1.30	0.2547
	Depart from Trend	8.29	0.0159
	Homogeneity	9.58	0.0225

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ON ORIGINAL

Source: C:\DATA\KEPRA\rat.dat

APPEARS THIS WAY
ON ORIGINAL

Table 6: PAIRWISE COMPARISONS BETWEEN COMBINED CONTROLS AND HIGH DOSE

FEMALE RATS
Sorted by Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
AD	Adrenals	14	cortical carcinoma	0.7558	0.5736	0.5738
AD	Adrenals	13	cortical adenoma	1.0000	0.8513	0.8514
AD	Adrenals	58	phaeochromocytoma - benig	1.0000	0.7508	0.7510
BN	Brain	5	astrocytoma	1.0000	0.6726	0.6729
CX	Cervix	42	malignant neurinoma	1.0000	0.7795	0.7797
KD	Kidneys	62	renal lipomatous tumour	0.3867	0.1039	0.1040
KD	Kidneys	61	renal carcinoma	1.0000	0.7864	0.7866
LY	Lymphoid/multicentric tum	40	lymphoid leukaemia	0.3855	0.1034	0.1035
LY	Lymphoid/multicentric tum	41	malignant lymphoma	0.7044	0.4957	0.4959
LY	Lymphoid/multicentric tum	26	histiocytic sarcoma	1.0000	0.8657	0.8658
LY	Lymphoid/multicentric tum	52	myeloid leukaemia	1.0000	0.7602	0.7604
MG	Mammary Glands	45	mammary adenoma	0.3867	0.1039	0.1040
MG	Mammary Glands	48	mammary fibroadenoma with	0.9455	0.8597	0.8597
MG	Mammary Glands	44	mammary adenocarcinoma	0.9526	0.9088	0.9089
MG	Mammary Glands	47	mammary fibroadenoma	0.9965	0.9933	0.9933
MG	Mammary Glands	49	mammary fibroma	1.0000	0.8862	0.8863
OV	Ovaries	42	malignant neurinoma	0.3867	0.1039	0.1040
	Ovaries	64	sertoli cell tumour - ben	1.0000	0.7864	0.7866
	Ovaries	65	sertoli cell tumour - mal	1.0000	0.7602	0.7604
PA	Pancreas	29	islet cell carcinoma	0.3867	0.1039	0.1040
PA	Pancreas	28	islet cell adenoma	1.0000	0.6726	0.6729
PW	Paws squamous cell papill	68	squamous cell papilloma	1.0000	0.7864	0.7866
PI	Pituitary	1	adenocarcinoma	0.7146	0.5705	0.5706
PI	Pituitary	2	adenoma	0.9815	0.9724	0.9724
PI	Pituitary	3	adenoma in pars anterior	1.0000	0.7614	0.7615
PG	Preputial Glands	1	adenocarcinoma	0.3867	0.1039	0.1040
SK	Skin	6	basal cell carcinoma with	1.0000	0.7864	0.7866
SK	Skin	30	keratoacanthoma	1.0000	0.7864	0.7866
SK	Skin	66	squamous cell carcinoma	1.0000	0.7864	0.7866
SC	Spinal Cord	5	astrocytoma	0.3214	0.0731	0.0732
ST	Stomach	32	leiomyoma - glandular reg	1.0000	0.6726	0.6729
SU	Subcutis	20	fibrosarcoma	0.6245	0.3717	0.3718
SU	Subcutis	18	fibroma	1.0000	0.7752	0.7753
SU	Subcutis	34	lipoma	1.0000	0.8862	0.8863
TL	Tail	12	chondroma	0.4286	0.1241	0.1242
TY	Thymus	70	thymic adenocarcinoma	1.0000	0.7542	0.7544
TH	Thyroids	56	parafollicular cell adeno	0.7752	0.5762	0.5764
TH	Thyroids	57	parafollicular cell carci	0.8703	0.7708	0.7708
TH	Thyroids	21	follicular adenoma	1.0000	0.9059	0.9059
TO	Tongue	72	undifferentiated carcinom	1.0000	0.7752	0.7753
	Uterus	16	endometrial stromal sarco	0.3867	0.1039	0.1040
	Uterus	42	malignant neurinoma	1.0000	0.7864	0.7866
T	Uterus	73	uterine adenocarcinoma	1.0000	0.7864	0.7866
A	Vagina	67	squamous cell carcinoma w	1.0000	0.7542	0.7544

Figure 1: Kaplan–Meier Survival Function

Species: Rat
Sex: Male

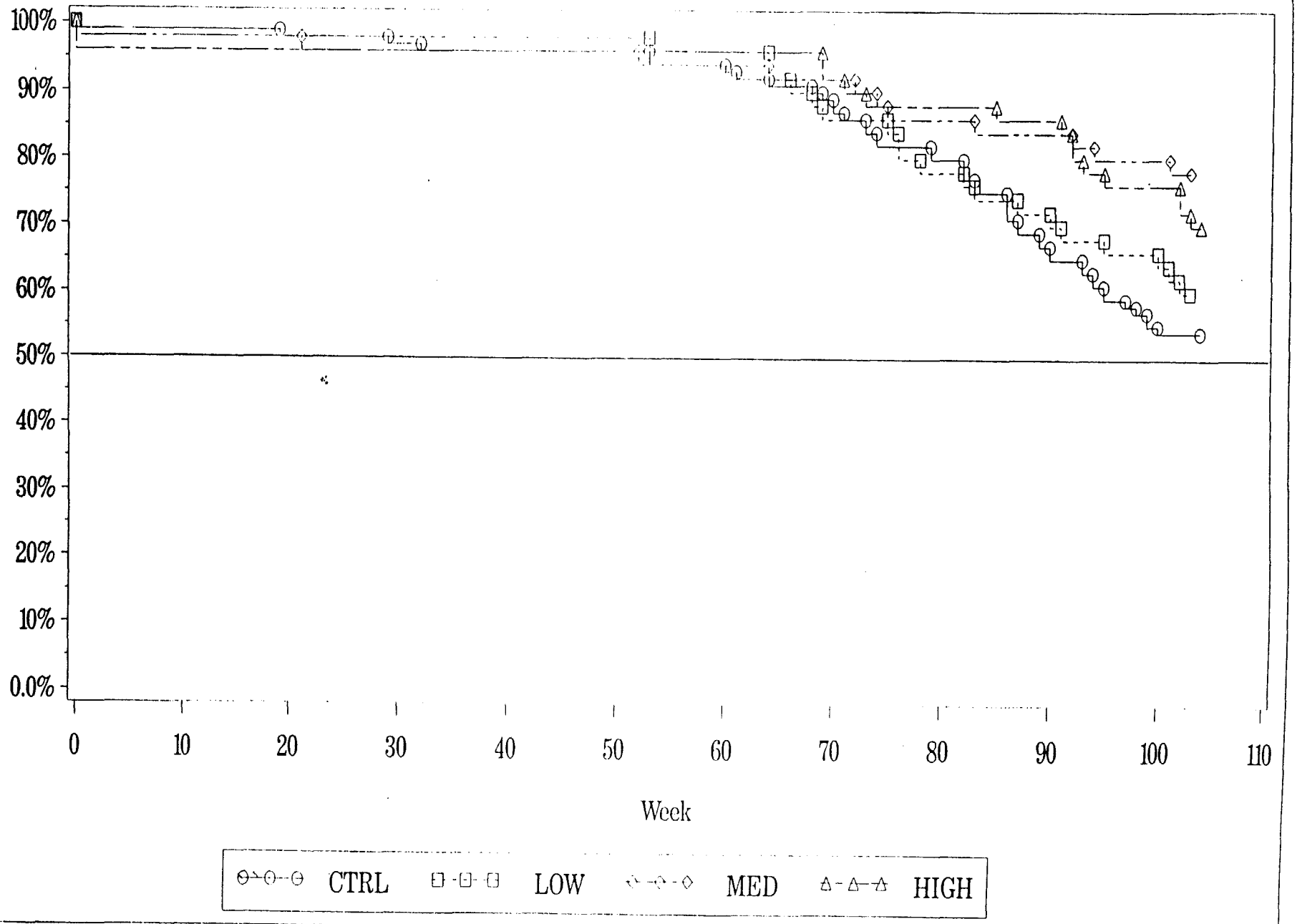

Figure 2: Kaplan–Meier S val Function

Species: Rat
Sex: Female

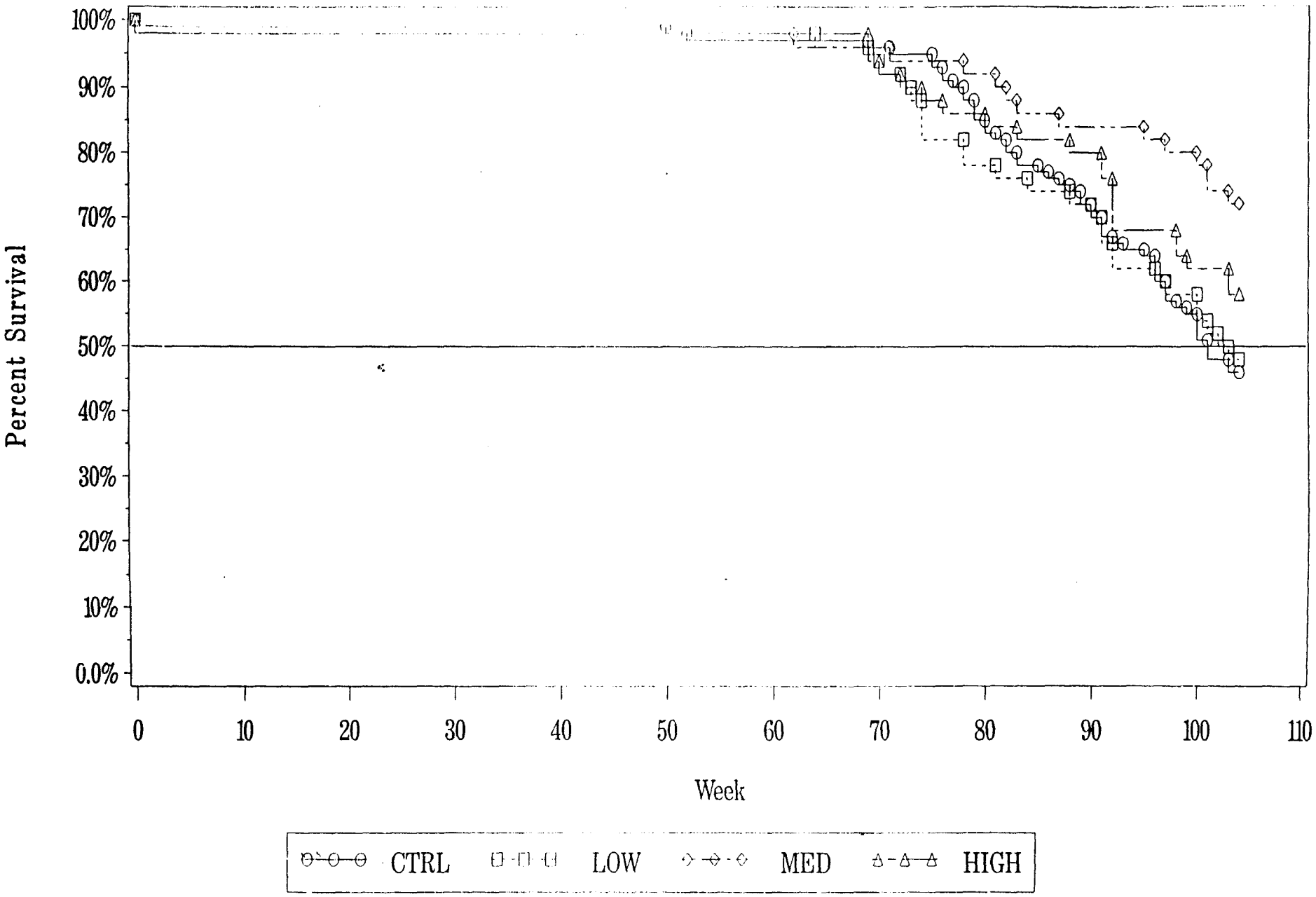

FIGURE 3 (from sponsor)

Bodyweights - group mean values Rats

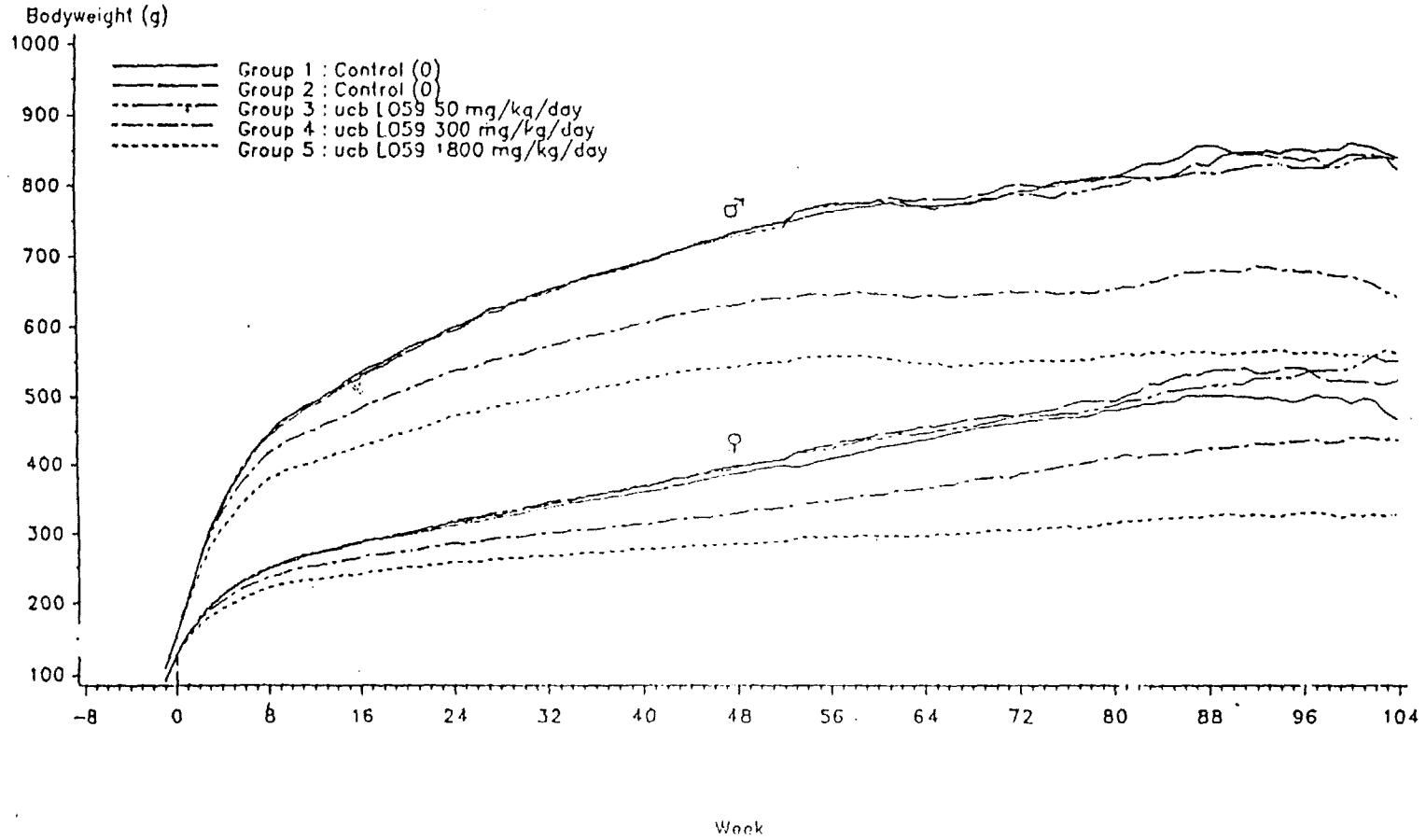

Table 7: Number of Animals
Species: Mouse
Sex: Male

Week	Treatment Group CTRL N	LOW N	MED N	HIGH N	Total N
0-52	3		1		12
53-68	9		6		24
69-80	23		6		48
81-82	69		39		176
Total	104		52		260

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ON ORIGINAL

Source: C:\DATA\KEPRA\mice.dat

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ON ORIGINAL

Table 8: Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.45	0.2293
	Depart from Trend	3.72	0.1556
	Homogeneity	5.17	0.1600
Kruskal-Wallis	Dose-Mortality Trend	1.51	0.2198
	Depart from Trend	4.24	0.1200
	Homogeneity	5.75	0.1246

Source: C:\DATA\KEPRA\mice.dat

Table 9: PAIRWISE COMPARISONS BETWEEN COMBINED CONTROLS AND HIGH DOSE

MALE MICE
Sorted by Organ Name

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
AC	Abdominal Cavity	10	Haemangiosarcoma	0.3551	0.0889	0.0891
HG	Harderian Glands	24	Cystadenoma	1.0000	0.7342	0.7346
LI	Liver	16	Liver cell tumour - malig	0.2540	0.1065	0.1066
LI	Liver	15	Liver cell tumour - benig	0.8749	0.8043	0.8044
LI	Liver	9	Haemangioma	1.0000	0.7710	0.7713
LL	Lungs	22	Pulmonary adenoma	0.5243	0.4309	0.4310
LL	Lungs	21	Pulmonary adenocarcinoma	0.5858	0.4833	0.4834
LY	Lymphoid/Multicentric tum	20	Pleomorphic lymphoma	0.3551	0.0889	0.0891
LY	Lymphoid/Multicentric tum	18	Malignant lymphoma	0.9244	0.8256	0.8258
PR	Prostate	1	Adenocarcinoma	1.0000	0.7710	0.7713
SK	Skin	4	Dermal fibrosarcoma	1.0000	0.7710	0.7713
SU	Subcutis	7	Fibrosarcoma	1.0000	0.7626	0.7630
TE	Testes	12	Interstitial cell tumour	1.0000	0.9546	0.9547

P (trend) Liver Cell tumor – malignant =0.1478

P (trend) Liver Cell tumor – benign =0.7869

P (trend) Liver Haemangioma =0.8477

Table 10, Number of Animals
Species: Mouse
Sex: Female

Week	Treatment Group CTRL N	LOW N	MED N	HIGH N	Total N
0-52	.		1		4
53-68	4		1		9
69-80	18		3		30
81-82	82		47		217
Total	104		52		260

Source: C:\DATA\KEPRA\mice.dat

Table II: Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.27	0.2599
	Depart from Trend	2.54	0.2809
	Homogeneity	3.81	0.2828
Kruskal-Wallis	Dose-Mortality Trend	1.36	0.2440
	Depart from Trend	2.49	0.2878
	Homogeneity	3.85	0.2784

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ON ORIGINAL

Source: C:\DATA\KEPRA\mice.dat

APPEARS THIS WAY
ON ORIGINAL

Table 12: PAIRWISE COMPARISONS BETWEEN COMBINED CONTROLS AND HIGH DOSE

FEMALE MICE
Sorted by Organ Name

APPEARS THIS WAY
ON ORIGINAL

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
HG	Harderian Glands	1	Adenocarcinoma	1.0000	0.7581	0.7585
HD	Head	6	Fibro-histiocytic sarcoma	0.3543	0.0885	0.0887
LI	Liver*	15	Liver cell tumour - benig	0.4947	0.2489	0.2491
LI	Liver*	9	Haemangioma	1.0000	0.7009	0.7014
LL	Lungs	22	Pulmonary adenoma	0.2614	0.1586	0.1587
LL	Lungs	21	Pulmonary adenocarcinoma	0.4375	0.2637	0.2639
LY	Lymphoid/Multicentric tum	18	Malignant lymphoma	0.2966	0.1887	0.1888
LY	Lymphoid/Multicentric tum	11	Histiocytic sarcoma	0.7343	0.5331	0.5334
LY	Lymphoid/Multicentric tum	20	Pleomorphic lymphoma	0.7758	0.6479	0.6481
MG	Mammary Glands	19	Mammary adenocarcinoma	1.0000	0.8948	0.8950
PI	Pituitary	3	Adenoma in the pars anter	0.3492	0.0861	0.0863
TH	Thyroids	8	Follicular adenoma	0.3571	0.0899	0.0900
UT	Uterus	13	Leiomyoma	0.5831	0.4141	0.4143
UT	Uterus	9	Haemangioma	1.0000	0.7706	0.7709
UT	Uterus	14	Leiomyosarcoma	1.0000	0.7706	0.7709

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ON ORIGINAL

* P (trend) Liver Cell tumor – benign = 0.3396

P (trend) Liver haemangioma = 1.0000

Figure 4: Kaplan–Meier S[illegible]val Function

Species: Mouse
Sex: Male

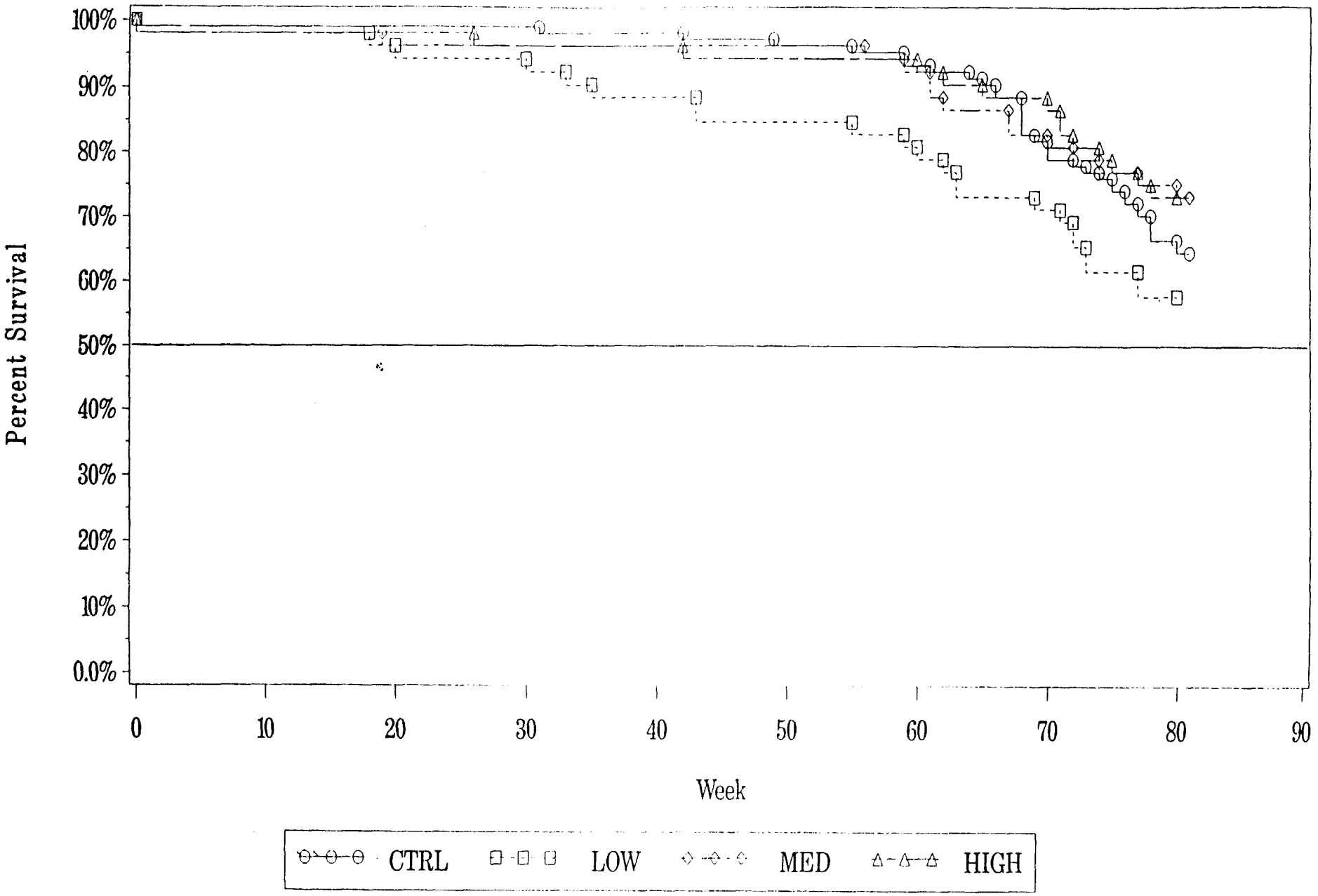


Figure 5 Kaplan–Meier [illegible]ival Function

Species: Mouse
Sex: Female

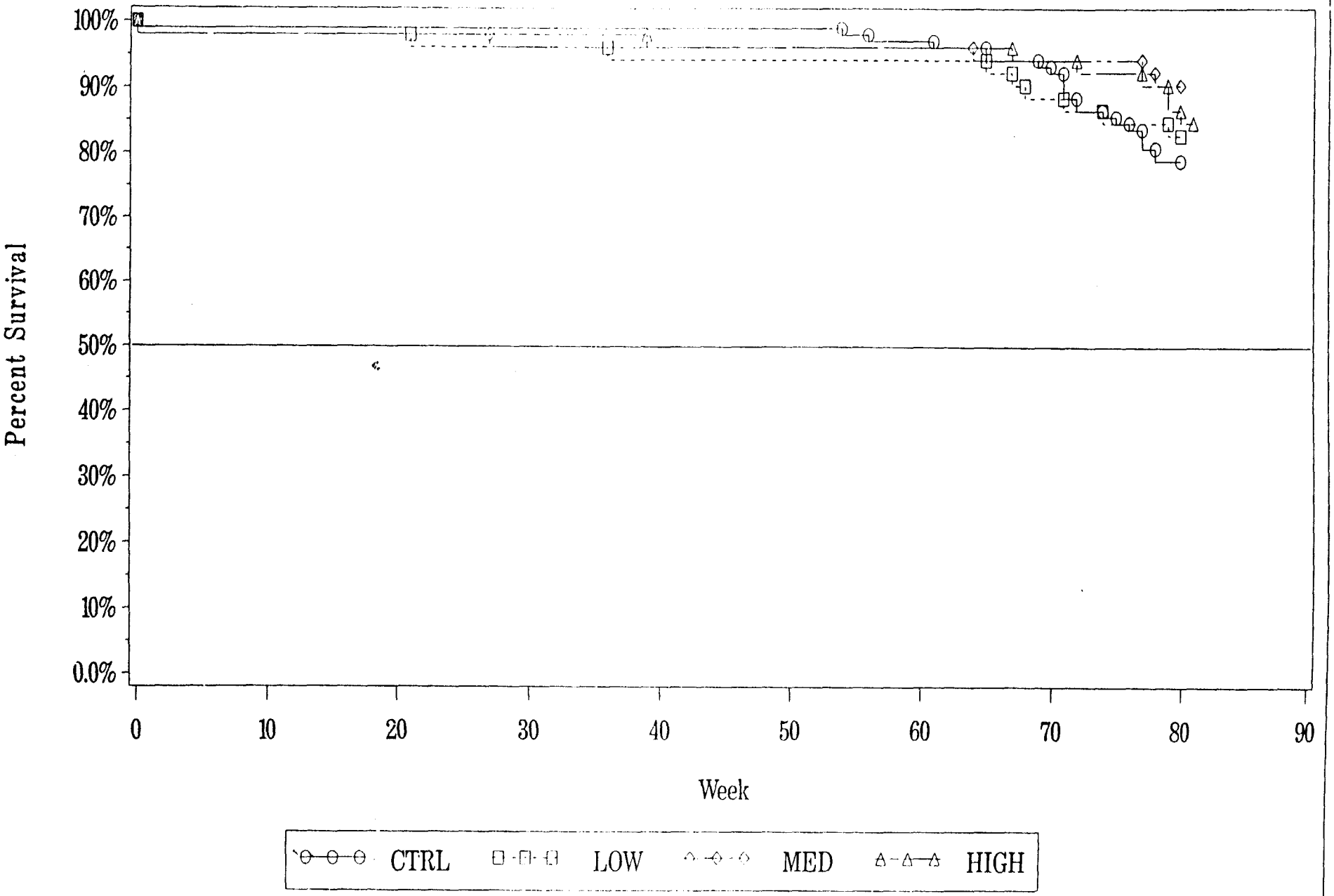
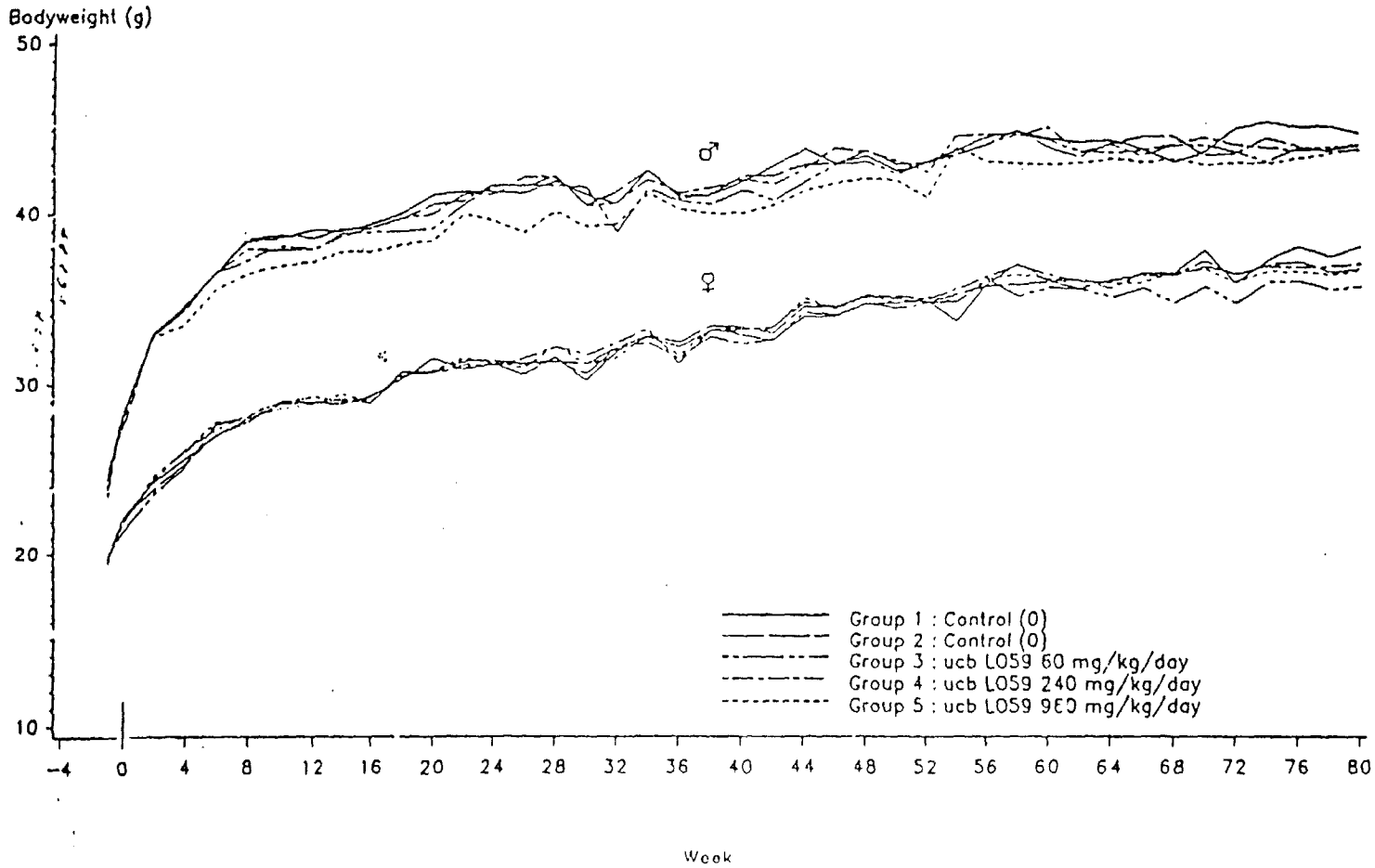


FIGURE 6

Bodyweights - group mean values



Executive CAC
21 September 1999

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Andrea Weir, Alternate Member
Glenna Fitzgerald, Team Leader
Jennifer A. Burris, Presenting Reviewer

Author of Minutes: JA Burris

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 21-035
Drug Name: levitiracetam
Sponsor: UCB Pharma Inc.

Mouse Carcinogenicity Study
80 week study ('89-'91); dose levels 60, 240, and 960 mg/kg admixed in diet. The committee discussed a number of study deficiencies, including the short duration, presence of drug contamination in control animal diet, and the lack of significant body weight reduction or toxicity in the high dose group. The committee agreed that there was no appropriate basis for dose selection i.e. an MTD was not achieved, body weights were not significantly reduced, no toxic endpoints were evident, exposures only exceeded that in humans by 2-5X. In addition, by current standards the study should have been extended to 104 weeks as survival was good at week 80.

Rat Carcinogenicity Study
104 week study ('89-'91); dose levels 50, 300, and 1800 mg/kg admixed in diet. The committee discussed a number of study deficiencies. These included drug contamination of control animal diet, large body weight reductions in the mid and high dose groups (↓20% and 30% respectively) with increased survival and without toxicity, and findings of the UK GLP audit particularly missing tissue samples. The dramatic reductions in body weight in the mid and high dose groups accompanied by reduced food consumption (↓5 and 10% in mid and high dose males; ↓5% in high dose females) were a major concern to the committee. Gavage studies at similar doses did not affect body weight or food consumption in studies up to 52-weeks (see CAC report addendum). This suggests that the loss of body weight with decreased feed intake in this drug-in-diet carcinogenicity study may have been due to reduced palatability. However, in a 26-week drug-in-diet study at similar doses, there was a loss of body weight without decreased food consumption indicating no palatability problem. The committee agreed that a more appropriate route of administration in this carcinogenicity study would have been by gavage. Despite a possible palatability problem, the toxicokinetic data demonstrated that increasing doses resulted in increased exposure, though less than a linear relationship. For example, at 102 weeks, rat AUCs were 275, 1158, and 3864 ug.h/mL respectively at the doses 50, 300, and 1800mg/kg – dose ratios were 1.0, 6.0, 36 and AUC ratios 1.0, 4.2, 14.1. The committee noted that exposures

in the highest dose in the rat study relative to human therapeutic doses were only 4-6X. In the rat low dose group, rat exposures relative to human were only 0.5-1.0X.

Executive CAC Recommendations and Conclusions:
The occurrence of control diet contamination in both studies was a concern. However, the very low levels of contamination and the small number of animals affected, as well as the clear lack of any positive tumor findings in both studies, lead the committee to conclude that this deficiency probably did not affect the outcomes of the studies.

The committee agreed that the mouse study was unacceptable, despite negative tumor findings, primarily because there was no appropriate basis for dose selection.

The committee agreed that the rat study is acceptable as a negative study pending any additional information from an ongoing European audit of UCB Pharma's analytical research facility in Belgium and an ongoing pathology peer review. There were no positive tumor findings, however the mid and high dose groups had increased survival, greatly reduced body weights, and decreased feed consumption possibly due to poor palatability (although see supervisory note in appended report). Gavage would have been the preferred route of administration because gavage studies, as opposed to drug-in-diet studies, did not affect body weight, and higher exposures may have been achievable.

Signed 10-04-99
Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:

Division File, HFD HFD-120
G. Fitzgerald, HFD-120
J. Burris, HFD-120
J. Frieman, HFD-120
M. Malandrucco, HFD-120
A, Seifried, HFD-024

ADDENDUM to CAC Report 21 Sep 99 **NDA 21-035** **J.A. Burris**

ORAL STUDIES IN THE RAT with Levitiracetam – Effects on Body Weight and Food Consumption

A. Studies with drug admixed in the diet
1. Palatability study in rats by dietary administration for one month (Engiish translation LE89C082, vol 30). SD rats dosed via continuos feeding admixed in the diet at 0, 22 67, 200, 600, and 1800 mg/kg/day. 9/sex/group. No effects on food consumption. Slight decrease in body

weights in both sexes at 1800 mg/kg/day in the later half of the study, though not statistically significant. Age at initiation of diet: 7-9 weeks. Study report concluded that the admixture of compound in the diet did not inhibit food intake/body weight gain.
2. 26-week toxicity study by repeated oral dosing (admixed with diet) with compound ucb L059 in the rat (RRLE91H1301 Vol. 34). SD rats, 21/sex/group, doses 0, 50, 160, 520, 1700 mg/kg/day. Body weights decreased in 520 and 1700 mg/kg males (6% and 10% respectively) and in the 1700 mg/kg females (10%). No consistent effects on food consumption.
3. Two year carcinogenicity study in SD rats (UCB 292/91989). Doses at 50, 300, and 1800 mg/kg/day. Body weights greatly reduced throughout the study in both sexes at 300 and 1800 mg/kg (20% and 30% respectively). Food consumption reduced in both sexes at 1800 mg/kg (5% in females, 10% in males) and in males at 300 mg/kg (5%).

B. Studies by oral gavage
1. Three month study in SD rats by gavage (report LE86L201, vol. 31) at 200, 600, and 1800 mg/kg/day. Body weights and food consumption slightly decreased in HDF without statistical significance.
2. (UCB #227/87415) 52-week toxicity in rats by oral gavage.
70, 350, and 1800 mg/kg/day. No effects body weights, food consumption.

Summary:

By **gavage** at doses similar to those used in the carcinogenicity study:
° 52 week study - no effects on body weight or food consumption
° 3-month study - minimal decrease in body weight and food consumption (HDF only)
By **admixture in the diet** at doses similar to those used in the carcinogenicity study:
°1-month study - minimal decrease in body weight (HDM&F), normal food consumption
° 26-week study -significant body weight reductions in HDM&F and MDM with no decreases in food consumption in
° 2-year study - significant body weight reductions in MD and HD both sexes with significant decreases in food consumption in HD M&F and MDM

Conclusions: The lack of adverse effects on body weight and food consumption in gavage studies versus the presence of these effects in drug-in-diet studies suggests that there may have been a palatability problem in the higher dose groups.

Supervisory note: The gavage studies call into question the source of the body weight effects in the carcinogenicity study as being related to drug palatability rather than toxicity. However, the absence of an effect on food consumption or body weight in the 1-month dietary admixture study, where palatability generally tends to be more predominant, decreases this concern. Also, palatability was not a problem in the 26-week dietary admixture study, in which decreases in body weight were not accompanied by decreased food consumption. GF 10-04-99.

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT
AND
FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET

P/T REVIEWER(s): Jennifer A. Burris
DATE: 21 September 1999

NDA: 21-035
DRUG CODE#: ucb L059
CAS#: 102767-28-2
DIVISION(s): Neuropharmacologic Drug Products
DRUG NAME(s): levetiracetam, Kepra

SPONSOR: UCB Pharma Inc, Smyrna GA, USA
LABORATORY: Huntington Research Centre, Huntington, UK
CARCINOGENICITY STUDY REPORT DATE: Mouse 4 March 1992; Rat 13 March 1992

THERAPEUTIC CATEGORY: anti-epileptic
PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: unknown mechanism, no class
MUTAGENIC/GENOTOXIC (y/n/equivocal/na; assay): No (Ames, E coli WP2uvrA, micronucleus, CHO/HGPRT, CHO metaphase chromosome, mouse lymphoma)

APPEARS THIS WAY
ON ORIGINAL

RAT CARCINOGENICITY STUDY:

RAT STUDY DURATION (weeks): 104
STUDY STARTING DATE: June 1989
STUDY ENDING DATE: June/July 1989
RAT STRAIN: SD
ROUTE: oral admixed in diet

NUMBER OF RATS:
- Control-1: 50/sex
- Control-2: 50/sex
- Low Dose: 50/sex
- Middle Dose: 50/sex
- High Dose: 50/sex

RAT DOSE LEVELS (mg/kg/day):
- Low Dose: 50
- Middle Dose: 300
- High Dose: 1800

BASIS FOR DOSES SELECTED: MTD – see attached review

PRIOR FDA DOSE CONCURRENCE: No CAC existed at the time

RAT CARCINOGENICITY: Negative

RAT TUMOR FINDINGS: None of interest

RAT STUDY COMMENTS: See attached review

MOUSE CARCINOGENICITY STUDY:

MOUSE STUDY DURATION (weeks): 80
STUDY STARTING DATE: 29 Aug 89
STUDY ENDING DATE: 20 Mar 91
MOUSE STRAIN: CD-1
ROUTE: oral admixed in diet

NUMBER OF MICE:
- Control-1: 52/sex
- Control-2: 52/sex
- Low Dose: 52/sex
- Middle Dose: 52/sex
- High Dose: 52/sex

MOUSE DOSE LEVELS (mg/kg/day):
- Low Dose: 60
- Middle Dose: 240
- High Dose: 960

BASIS FOR DOSES SELECTED: MTD - See attached review

PRIOR FDA DOSE CONCURRENCE: No CAC existed at the time

MOUSE CARCINOGENICITY: Negative

MOUSE TUMOR FINDINGS: None of interest

MOUSE STUDY COMMENTS: See attached review

MOUSE CARCINOGENICITY:

Study Title: Potential tumorigenic effects in prolonged dietary administration to mice
Study Number: RRLE91K0702, UCB 293 91890
Volume Numbers: 53-57
Test Facility: [redacted]
Study Date(s): treatment initiated 29 Aug 89, necropsies completed 20 Mar 91 (80 week study)
Date of Submission – previously submitted with IND (1994) but not reviewed
GLP Compliance/Quality Assurance: Yes (confirmed by UK GLP Monitoring Authority audit)
QA Report- Yes (X)
Study Type: carcinogenicity, oral admixed in the diet
Species/strain: mouse/Crl:CD-1 (ICR) BR
Number of animals per group; age at start of study: 52/sex/group; 3-4 weeks old
Animal housing: 4/cage (sexes separate), solid plastic cages with sawdust bedding
Drug Lot/Batch number(s): 900
Drug Purity / Stability / Homogeneity: Stable at room temperature (in darkness) for three years. Fresh mixtures for the diet prepared every two weeks. White crystalline powder [redacted] Homogeneity/concentrations verified prior to and during the study at 3 month intervals.
Doses: 0, 0, 60, 240, 960 mg/kg/day

- Basis of Dose Selection: 13-week study in mice (report UCB #311/891682, vols. 28-9). 15/sex/group, same strain, doses 0, 60, 240, 960, 3840 mg/kg/day. No treatment related mortality. Reduced body weights in both sexes at 3840 mg/kg (M 7%, F 9%) and as well as females at 960 mg/kg (7%). Reduced body weight gains in both sexes at 3840 mg/kg/day also in females at 960 mg/kg/day. Normal food consumption but reduced efficiency of food utilization (food intake per unit gain in body weight) in 960/3840 mg/kg females. Increased liver weights in both sexes at 3840 mg/kg/day also in males at 960 mg/kg/day. Increased incidence of centrolobular hepatocyte enlargement and vacuolation in both sexes at 240, 960, and 3840 mg/kg/day (moderate at 3840, minimal at other doses). NOAEL 240 mg/kg/day. Highest dose selected for carcinogenicity bioassay 960 mg/kg/day based on body weight reductions/liver pathology.
- Relation to Clinical Use: Repeat dose AUC in patients are 273 and 640 ug.h/mL at the recommended low and high doses of 20 and 60 mg/kg day. AUCs in mice at 78 weeks were (M/F average) 65, 314, 1505 ug.h/mL respectively for the dose groups 60, 240, 960 mg/kg/day. Mouse exposure in the highest dose group relative to the human low/high dose is 5.5X/2.4X.
- CAC Concurrence: CAC did not exist when this study was initiated.
- Route of Administration: oral admixed in diet
- Frequency of Drug Administration: continuous in diet
- Dual Controls Employed: Yes, two control groups (groups 1,2), each 52/sex
- Interim Sacrifices: None
- Satellite PK or Special Study Group(s): None
- Unscheduled Sacrifices or Deaths: Occurred, of course, however no apparent relation to treatment and not unreasonable losses.

Study Results:

- Clinical Observations: Dose related increased incidence of yellow urogenital staining in mid and high dose groups of both sexes.
- Mortality: Mortality was unaffected by treatment. Survival was more than adequate in all groups to week 80 (avg. survival 67% males, 83% females).
- Body Weight: Body weights (group means) for the male high dose group were consistently depressed from week 5 throughout the study (approximately 3-5%). The male high dose group also had depressed body weight gains (21% when compared to combined controls) over the first 26 weeks. The male mid dose group had depressed body weight gains (33%) over the latter two-thirds of the study (weeks 26-80). Body weights (group means) for all female groups were similar throughout the study. All female treated groups had increased body weight gains (13-25%) in the first 26 weeks but depressed body weight gains (13-25%) from weeks 26-80 of the study. Weights were recorded weekly.
- Food Consumption: No treatment related effects. Measured weekly.
- Hematology: High dose groups, both sexes, had statistically significant decreases in total WBC counts, neutrophils and lymphocytes at week 80. These were well within normal ranges and of no biological significance. Blood samples (orbital) collected at week 52 (not analyzed) and at termination, as well as at any interim euthanasia.
- Organ Weights, Clinical Chemistry, Ophthalmology: Not done.
- Gross Pathology: Dose related fur staining in the genital region (apparently, the same "yellow urogentital staining" noted during clinical observations) in all male dose groups and in the high dose female group. Dose related distention of seminal vesicles in male mid and high dose groups.
- Histopathology: Done on all indicated tissues (see tissue list below) of all control and high dose mice. Also, tissues of low and mid dose mice which died during the study. Done only on selected tissues of low and mid dose mice at termination (livers and gross lesions).

  Non-Tumor – Increased incidence and severity of moderate to marked centrolobular hepatocyte enlargement in the high dose male group. Increased incidence of minimal to moderate centrolobular hepatocyte vacuolation in the high dose male group. Individual high dose males with centrolobular hepatocyte vacuolation also had centrolobular hepatocyte enlargement. Increased incidence of centrolobular hepatocyte vacuolation but not enlargement in mid and high dose females. The clinical and gross abnormalities of urogenital staining and distended seminal vesicles had no microscopic correlates.

  Tumor – No treatment related increased incidence of neoplasms or pre-neoplastic lesions. No unusual neoplasms. No decreased tumor latency or enhancement of tumor progression.
- Toxicokinetics: Blood for drug level assays collected at week 78 from 20/sex/group and at week 80 from all remaining animals. Study # RRLE91K2201 "Plasma concentrations of ucb L059 in mice following repeated oral dietary administration." Blood samples from mice in this carcinogenicity study obtained at week 78 from 10/sex/group and at study termination from all available mice (then frozen, sent

to Belgium for analysis). In treated groups, plasma concentrations in males exceeded females (approximately 1.5:1), plasma concentrations approximately linearly related to the nominal doses in both sexes. No apparent accumulation (in plasma) with chronic administration. No drug was detected in week 78 samples from control groups (two control groups, each 52 animals). At terminal sacrifice (week 80) low drug levels were detected in a small number of control group 1 animals of both sexes (6/35 males, 6/40 females, total 12/75). Of these twelve animals, levels in ten were less than 0.50 ug/ml, the lowest limit of reliable detection, two animals had levels at 1.10 and 0.59 ug/ml). Diet analysis throughout the study was uneventful. Study report concluded that contamination, most likely during weekly formulation and/or admixture of pre-mix, had occurred "at the end of the study." The possibility that these errors occurred at other points throughout the study cannot be dismissed which may have resulted in contamination of control diet with drug throughout the study.

Overall Interpretation and Evaluation:

- Adequacy of the carcinogenicity studies and appropriateness of the test model: Appropriate route. Appropriate species. NOEL was 60 mg/kg/day based upon microscopic findings in the liver and depressed body weights/body weight gains. Did not achieve an MTD however the dose levels were selected appropriately based upon body weight and body weight gain in the 13-week study. Very close to an MTD (based on body weight and body weight gain) in males on this study but not females. Due to good survival, study could have been continued another month or longer. Possible contamination of control diet with drug at low levels in small numbers of animals may have occurred throughout the study (facts: did occur at week 80, did not occur at week 78).
- Evaluation of Tumor Findings: No positive findings.
- Statistical Reviewer Comments (R. Kelly): Statistical evaluation agrees with that in study report. No tumor findings reached statistical significance. Questions validity of protocol that terminated the study at 80 weeks despite excellent survival. Agrees that male high dose very close to an MTD but not females.

Summary Conclusions:

- Acceptability of Study(s) or Overall Testing Approach: Acceptable. Clearly, the dosing could have been higher (not predicted by range-finding study) and the study could have been longer (80 weeks/18 months has been a standard for the mouse). Contamination of control animal diet may have occurred in various animals at very low levels at varying times throughout the study. Despite these deficiencies in the study, the lack of any even borderline positive tumor findings indicates that this drug does not cause cancer in mice.
- Major Tumor Findings: None
- Non-neoplastic Findings: Reduced body weights and body weight gains in male high dose group. Liver pathology (centrolobular hepatocyte hypertrophy/vacuolation) in high dose groups (M>F) probably adaptive however toxicity/adversity of these findings are difficult to evaluate with no clinical pathology/organ weight data.

RAT CARCINOGENICITY:

Study Title: Potential tumorigenic and toxic effects in prolonged dietary administration to rats
Study Number: UCB 292/91998
Volume Numbers: 57-63
Test Facility: [redacted]
Study Date(s): June 1989 (first dosing) - June/July 1991 (weeks 104-105)
Date of Submission: previously submitted with IND (1994) but not reviewed
GLP Compliance/Quality Assurance: Yes (confirmed by UK GLP Monitoring Authority audit)
Study Type: carcinogenicity, 104 weeks
Species/strain: Crl:CD (SD) BR rats
Number of animals per group: Four groups, 50/sex/group (main) and 20/sex/group (satellite for blood/interim sacrifice terminated at 52 weeks)
Animal housing: 5/cage
Drug Lot/Batch number(s): 900
Drug Purity / Stability / Homogeneity: Stable at room temperature (in darkness) for three years. Fresh mixtures for the diet prepared every week. White crystalline powder [redacted]
Homogeneity/concentrations verified prior to and during the study at 3-month intervals.

Doses: 0, 0, 50, 300, 1800 mg/kg/day

- Basis of Dose Selection: UCB #227/87415 52-week toxicity in rats by oral gavage. 70, 350, and 1800 mg/kg/day. (Reviewed in '94). No effects on survival, body weights, food consumption. Liver and kidney target organ toxicity in males and females at 1800 mg/kg included increased weights, gross enlargement, centrolobular hepatocyte enlargement/vacuolation, progressive glomerulonephritis with renal tubular cytoplasmic eosinophilic inclusions (males only).
- Relation to Clinical Use: Repeat dose AUC in patients are 273 and 640 ug.h/mL at the recommended low and high doses of 20 and 60 mg/kg day. AUCs in rats at 102 weeks were (M and F averaged) 275, 1158, and 3864 ug.h/mL respectively for the dose groups 60, 240, 960 mg/kg/day. Rat exposure in the highest dose group relative to the human low/high dose is 4.2X/6.0X.
- CAC Concurrence: No CAC existed at the time.
- Route of Administration: oral admixed in the diet
- Frequency of Drug Administration: continuous in the diet
- Dual Controls Employed: yes
- Interim Sacrifices: at 52 weeks (20/sex/group satellite for bleeding)

Study Results:

- Clinical Observations - Increased incidence of yellow urogenital staining in high dose groups, both sexes.
- Mortality: Control group 2 males and control group 1 females had increased mortality (56 and 58% respectively). mid and high dose groups of both sexes had reduced mortality (22 and 30 % males, 28 and 42% females) over the course of the study.

- Body Weight: mid and high dose groups of both sexes had greatly reduced body weights throughout the study (18 and 27% males, 20 and 33 % respectively). Body weight gains were significantly reduced in mid and high dose groups of both sexes in the first 52 weeks of the study.
- Food Consumption: Reduced in mid and high dose males (first 52 weeks). Achieved drug intakes were acceptably close to nominal levels.
- Ophthalmoscopy: No treatment related findings at weeks 52 and 103 (control group 1 and high dose groups only examined).
- Hematology: No treatment related findings (weeks 13, 26, 52, 78 and 104).
- Clinical Chemistry: Increased BUN, total protein, and globulin in high dose males. Increased GOT, GPT in high dose males and females.
- Urinalysis: Decreased pH in high dose males and females.
- Organ Weights: (adrenals, brain, heart, kidneys, liver, ovaries, pituitary, testes, thyroid weighed). Increased liver and kidney weight in high dose groups, both sexes. Increased kidney weight also in mid dose females. Decreased weights of testes/epididymes in all treated males.
- Gross Pathology: Increased incidence of urogenital staining of the hair in both high dose groups. Increased incidence of pale kidneys in high dose males.
- Histopathology: Done on control and high dose animals at interim and terminal sacrifice. Also, all animals from any group dying on study, all tissues from any group with gross abnormalities. Any tissue/organ in the high dose with an identified possible treatment related change was also examined in the low and intermediate groups. See tissue list below.

  Non-Tumor: Liver – minimal to moderate centrolobular hepatocyte enlargement with vacuolation in all treated groups (dose related increased incidence and severity in males; dose related increased incidence but not severity in females), minimal to moderate generalized hepatocyte enlargement only detected in high dose males, increased incidence of centrolobular hepatocyte fat in high dose males. Liver EM – smooth ER proliferation in centrolobular and periportal hepatocytes of high dose groups both sexes but not low dose groups (mid dose not sampled). Testes – dose related increased incidence of tubular atrophy in all treated male groups. Kidney – dose related increased incidence and severity of esosinophilic intracytoplasmic droplets/granules in cortical tubules in mid and high dose males, dose related increased incidence cortical tubular basophilia in mid and high dose males, medullary mineralization detected only in mid and high dose males with greater incidence and severity at high vs. mid doses, corticomedullary junction mineralization only detected in high dose males, reduced incidence and severity of progressive glomerulonephritis (a.k.a. nephropathy) in mid and high dose groups of both sexes (probably related to reduce body weights in these groups).

Tumor: Body weight losses with increased survival in mid and high dose groups may have influenced tumor incidence. Reduced incidence of common tumors (pituitary adenomas, mammary fibroadenomas) in mid and high dose groups. No treatment related increased incidence of neoplasms or pre-neoplastic lesions. No unusual neoplasms. No decreased tumor latency or enhancement of tumor progression.

- Toxicokinetics: Study RRLE91M1101 "plasma concentrations of ucb L059 in rats following repeated oral dietary administration at various dosage levels" (study on the potential tumorigenic effects of ucb L059 to rats, UCB 292). Plasma concentrations lower in females than males in general. Plasma concentrations and AUCs approximately linearly related to the nominal dose up to 300 mg/kg. Plasma concentrations/AUCs were lower than would be expected at 1800 mg/kg. Reliably measured down to concentrations of 0.10 ug/ml. Low levels of drug were detected in both sexes from both control groups in small numbers of animals at all time points sampled. Week 52 control group 1, 2/10 animals at or below limit of detection (0.10 ug/ml). Week 52 control group 2, 2/10 animals at 0.20 and 0.50 ug/ml. Week 60 control group 1 (n = 4/10 animals) and control group 2 (n = 3/10 animals), 5 animals at or below the limit of detection, 2 animals at 0.20 and 0.30 ug/ml. Week 102, control group 1 had 8/40 tested with detectable drug levels (3 under 0.50 ug/ml, three at 0.60, one at 0.8, one at 1.0ug/ml. Week 102, control group 2 - only 1/40 (0.60 ug/ml). Example plasma concentration (group means) at 50, 300, and 1800 mg/kg dose respectively 12, 50, and 170ug/ml. Study report concludes that "there was some sporadic low contamination which occurred in a few samples from control animals and/or that some interferences were present in the samples." The possibility that some control animals (varying from 20% to 40%) had low levels of drug (generally at or below the limit of detection) in the diet at various time points throughout the study cannot be dismissed.

Overall Interpretation and Evaluation

- Adequacy of the carcinogenicity studies and appropriateness of the test model: Appropriate route. Appropriate species. NOAEL 50 mg/kg/day based upon body weights, renal and hepatic pathology. Large decreases in body weight in mid and high dose groups resulted in decreased mortality, reduced common tumor burden (pituitary/mammary adenomas), and reduced incidence/severity of common non-neoplastic conditions (progressive nephropathy). MTD exceeded at the mid and high doses based on body weights but not mortality (survival prolonged likely due to the reduction in incidence and severity of progressive nephropathy). The fact that some control animals (varying from 20% to 40%) had low levels of drug (generally at or below the limit of detection) in the diet at various time points throughout the study leads one to question the validity of the entire study (as in the mouse study).
- Evaluation of Tumor Findings: No positive findings.
- Statistical Reviewer Comments (R. Kelly): Statistical evaluation agrees with that in study report. No tumor findings reached statistical significance. High dose exceeded the MTD based on body weight.

Summary Conclusions and Recommendations

- Acceptability of Study(s) or Overall Testing Approach: Acceptable. MTD exceeded but mortality decreased. The tumor burden may have been favorably affected by the great decreases in body weight, and possible low level contamination of diet in some of the control animals is problematic, however the lack of any even borderline positive tumor findings indicates that this drug does not cause cancer in rats.
- Major Tumor Findings: None
- Non-neoplastic Findings: Decreased body weights and mortality in mid and high dose groups. Hepatotoxicity - increased GOT/GPT and liver weights in high dose males and females, generalized hepatocyte hypertrophy with centrolobular hepatocyte fat accumulation in high dose males. Renal toxicity - increased BUN with pale kidneys and increased kidney weights in high dose males, increased incidence and severity of α-2-microglobin in cortical tubules in mid and high dose males.

MOUSE AND RAT CARCINOGENICITY – Study Audits by EMEA:

By letter dated July 16, 1999, UCB Pharma informed FDA that the European Agency for the Evaluation of Medicinal Products (EMEA) suspended review of the licensing application for ucb L059. This action was taken pending audits of the above rat and mouse carcinogenicity studies (and the 13-week range finding study for dose determination in the mouse). This action was due primarily to the presence of drug levels in plasma of some untreated control animals in all of these studies.

There were a number of other discrepancies/problems identified such as: seven tissues in the rat study (3 liver, 2 kidney, 1 pituitary, 1 uterus/cervix from control and low dose females/low and mid dose males) reported as "normal" in the study report were reported as "missing" by the peer review pathologist, one additional study (immunostaining of male rat kidneys for α-2-microglobulin) had no protocol or amendment therefore not considered to be a GLP study, no abbreviation glossary in the study report, humidity during the study deviated from that in the protocol, and so on.

In an amendment to this NDA dated August 31, 1999, UCB Pharma provided an update on the status of this investigation which included the audit report by the UK GLP Monitoring Authority as well as Huntington Life Sciences' response to the audit report. The auditors found no GLP deviation which could account for the presence of test substance in the plasma of untreated animals however it could not be excluded that control animals had been exposed to the test substance due to mix-ups and contamination of feeds (or processing or analysis of plasma). The auditors discovered that the tissues read as "normal" by the study pathologist found to be "missing" by the peer review pathologist had not been read by the study pathologist and had never been processed – this was regarded as a significant deviation from GLP. The UK auditors concluded that, despite some deficiencies, overall this study had been conducted in compliance with the Principles of GLP. Huntington Life Sciences compared control animal tumor incidence

data in these studies to data from other studies at their lab and found no differences (however no comment was made if these other studies did or did not have drug detected in control animal plasma).

Three additional evaluations are being conducted and will be submitted to the agency sometime in October '99 – an independent audit by EPL of UCB's analytical lab in Belgium (where the plasma samples were analyzed), an audit of this facility and the three analytic studies by the Belgian GLP Monitoring Authority, and an independent peer review of slides from the rat carcinogenicity study.

Histopathology Inventory

Study	Carc.	Carc.		
Species	Mouse	Rat		
Adrenals	•	x		
Aorta				
Bone Marrow smear				
Bone (femur)	•	x		
Brain	• 3 areas	x 3 areas		
Cecum	•	x		
Cervix	•			
Colon	•	x		
Duodenum	•	x		
Epididymis	•	x		
Esophagus	•	x		
Eye	•	x		
Fallopian tube				
Gall bladder				
Gross lesions	•			
Harderian gland				
Heart	•	x		
Hyphophysis				
Ileum	•	x		
Injection site				
Jejunum	•	x		
Kidneys	•	x		
Lachrymal gland				
Larynx				
Liver	•	x		
Lungs	•	x		
Lymph nodes, cervical	•	x		
Lymph nodes mandibular				
Lymph nodes, mesenteric	•	x		
Mammary Gland	•	x		
Nasal cavity				
Optic nerves				
Ovaries	•	x		
Pancreas	•	x		
Parathyroid	•	x		
Peripheral nerve				
Pharynx				
Pituitary	•	x		
Prostate	•	x		
Rectum	•	x		
Salivary gland	•	x		
Sciatic nerve	•	x		
Seminal vesicles	•	x		
Skeletal muscle	•	x		
Skin	•	x		
Spinal cord	•	x		
Spleen	•	x		
Sternum	•	x		
Stomach	•	x		
Testes	•	x		
Thymus	•	x		
Thyroid	•	x		
Tongue	•	x		
Trachea	•	x		
Urinary bladder	•	x		
Uterus	•	x		
Vagina	•			
Zymbal gland				