EVALUATION & RECOMMENDATION:

There were several studies done with CL 284-846 to determine doses for the life-time carcinogenicity studies in the rat and mouse. They included more than 1 strain in the mouse as well as 2 routes of administration: gavage and dietary. Following several correspondances between the sponsor and the Division starting in May 1992, the following doses were studied: for the **rat dietary study: 1, 10, and 20mg/kg,** and for the **mouse dietary study: 25, 50, 100, and 200mg/kg** in males and females. A 2yr **mouse gavage** study was initiated by the sponsor without concurrence from the Division or the CAC; basis for dose selection was AUC, a parameter that was not deemed appropriate by the Division. The doses selected for the mouse gavage study were **1, 5, and 20mg/kg/d.** Shortly after initiation of this study, the sponsor proposed raising the high dose from 20 to 50mg/kg/d, the Division was not in favor of this and a final agreement was reached that the doses for the mouse gavage study be **10, 40, 80mg/kg for males and 25, 100, 200mg/kg for females.** This study was continued only for 42wks due to excessive deaths mainly in high dose.

The dose selection particularly for high dose in the dietary carcinogenicity studies for both rat and mouse, based on the findings in these 2 species, seems appropriate. Considering the liver as the target organ of toxicity for this drug, liver weight was **NOT** determined in the 2yr dietary mouse study, such measurements would have supported or, not supported, the liver adenomas noted in female mice dosed 200mg/kg. In **NONE** of the carcinogenicity studies, clinical chemistry or urinalysis, were assessed at any time; these are usually standard parameters determined during a life-time bioassay.

Based on the results of the dietary carcinogenicity studies in mice and rats, the justifications presented by the sponsor for the findings of liver adenomas in mice at 200mg/kg/d, to be caused by an indirect mechanism of CL 284-846 on liver cells may be acceptable. The 200mg/kg dose represents 1176x the maximum recommended human dose per day on a mg/kg basis or 95x on a mg/m^2 basis. The sponsor suggested that the liver adenomas in mice are caused by an "epigenetic" mechanism based on the following justification/reasoning:

- the liver adenomas were found in female mice and not males (exceeded historical control range),
- the finding was not dose dependent, seen only at the high dose of 200mg/kg,
- only in mice not in the rat,
- no liver hyperplasia or carcinomas were seen in these animals or any other animals),
- No liver adenomas in males kept for 4wk recovery following 65wk of daily dietary dosing (incidence comparable to cont),
- CL-284-846 is not mutagenic cpd in 2 in gene mutation assays.
- the sponsor referrenced the literature including studies and conclusions by the NTP indicating that "findings of liver tumors in mice only, does not carry the same weight for human risk as a trans-species, multiple site carcinogenic response". Similar conclusions have been published in the literature including the ICH (FR notice, Aug 1996).
- the induction of the liver adenomas maybe an epi-genetic and indirect mechanism.

Other effects of CL 284-846 included death, inconsistant effect on mean wt and/or wt gain with or without increase in food intake, and, in general, increase in liver wt (absol and/or rel). Liver centrilobular hypertrophy occurred in all 3 rat 3mo dose range finding studies (diet and gavage), in the mouse 3mo diet and 5mo gavage studies (not in the 3mo dietary study using C57BL/6NCrlBR strain), and in the mouse car studies; no liver hyperplasia or carcinomas were seen in these animals at incidences that exceeded the concurrent or historical control range.

It is the reviewer's opinion however, that the sponsor's conclusion that zaleplon is not mutagenic, is arguable. Zaleplon was clastogenic in presence and/or absence of metabolic activation, causing structural and numerical aberrations (polyploidy and endoreduplication) when tested in the Chinese hamster ovary cells and human lymphocyte chromosomal aberration assays. Therefore, a possible mutagenic mechanism of induction of liver adenomas can not be ruled out.

STATISTICAL REVIEW AND EVALUATION

NDA: 20-859. Pre-Clinical Studies (Carcinogenicity Evaluation)
Applicant: Wyeth-Ayerst.
Name of Drug: CL 284,846 (Sonata, Zaleplon, capsule)
Document Reviewed: Volumes 1.58, 1.59, 1.73, and 1.74, received 8/6/98

OCT 19 1998

1. INTRODUCTION

The sponsor has submitted a report containing details of the results of analyses of data collected for both mouse and rat studies together with diskettes containing this data. These two studies were intended to assess the carcinogenic potential of Zaleplon in mice and rats. Zaleplon was administered orally in dietary mixture at some selected dose levels. The duration for both the mouse and the rat studies was 104 weeks.

2. MOUSE STUDY (# 450)

2.1. Design

In this study an experiment was conducted in which 450 female and 450 male CD-1 mice were observed for carcinogenicity under specified laboratory and dietary conditions for 24 months. These animals were randomly divided into six groups of equal sizes to receive different dose levels of Zaleplon (in dietary admixture): 0, 0, 25, 50, 100, and 200 mg/kg/day. These dose levels will be known as first control, second control, low, medium, medium high, and high, respectively. The animals were observed daily for mortality and morbidity and were examined weekly for the presence of masses. At the end of the study all surviving animals were necropsied and microscopically examined.

2.2. Sponsor's analysis

Survival analysis

The sponsor has applied log-rank test and trend analysis using ordinals (0, 1, 2, 3, 4) and dose proportionals (0, 25, 50, 100, 200). The sponsor reported that there was a significant decrease in dose related survival (p-value=0.04 for males and 0.004 for females). A summary of the survival and deaths distributions is given in Table 1.

Survival curves for male and female mice are shown in figures 1 and 2, respectively.

Tumor data analysis

The sponsor has applied exact tests (the log-rank test for fatal tumors and Mantel-Haentzel test for incidental tumors) and Peto's test (Peto and al. 1980) for the combined fatal and incidental

tumors for each tumor type. These trend tessts were applied using both dose proportionals and dose ordinals. Table 2 presents the significant results for the incidence of tumors for Zaleplon doses versus the controls.

2.3. Reviewer's Analysis

FDA Statistical Decision Rules

FDA classifies a tumor as a "common" tumor if the incidence rate is >1% and as a "rare" tumor if the incidence rate is ≤1%.

The decision rules which FDA statisticians follow are summarized below.

1. For common tumors, the level of significance used in pairwise comparisons is α =0.01 and in trend analysis the level of significance used is α =0.005.

2. For rare tumors, the level of significance used in pairwise comparisons is α =0.05 and in trend analysis the level of significance used is α =0.025.

Survival analysis

This reviewer has carried out a homogeneity analysis and a trend analysis on the survival data for male and female mice separately, using two statistical methods. The first method used Cox's statistic for life tables (see reference 2 or 4) and the second used Kruskal-Wallis statistic for survival data (see reference 2 or 5). Both Cox's and Kruskal-Wallis statistics use a Chi-square test, weighted with a calculated variance-covariance matrix, that is derived from an observed life table but, the difference between the two statistics is that the latter gives more weight to early deaths. The homogeneity analysis carries out the testing of the hypothesis of equality of survival distributions among the treatment groups and the trend analysis carries out the testing of the hypothesis of a linear trend in the survivals among the treatment groups of animals.

The results of analysis confirm the sponsor's results that show a significantly decreasing dose related trend in survival for both nale and female nice.

Tumor data analysis

This reviewer has carried out a trend analysis, using FDA's approach (which is implemented in a SAS program) for analyzing the incidence of tumor for Zaleplon doses versus the combined control (placebo). This program employs the same statistical method the sponsor applied in the trend analysis (Peto et al (1980)) for the combined fatal and incidental tumors using dose proportionals. The purpose of this analysis is to see if there is an increase (or decrease) in the number of animals who show tumors as the dose level increases from the lowest (control) to the

highest dose. The results of analysis for female and male mice are shown in Tables 3 and 4, respectively. Tables 3 and 4 show similar results as those found by the sponsor.

According to the FDA's rule stated above, only the following tumor types in female mice are considered significant.

Adenoma,hepatocellular (Liver) (p-value<0.001), and
Fibrosarcoma or sarcoma (skin) (p-value=0.02).

3. RAT STUDy (#419)

3.1. Design

In this study an experiment was conducted in which 300 female and 300 male rats were studied for carcinogenicity under specified laboratory and dietary condition for 24 months. Males (as well as females) were randomly divided into four groups of sizes 120, 60, 60, and 60 animals to receive the dose levels of Zaleplon (in dietary admixture) 0, 1, 10, and 20 mg/kg/day, respectively. These dose levels were known as control, low, medium, and high, respectively. The animals were observed daily for mortality and morbidity and were examined weekly for the presence of masses. At the end of the 24 months all surviving animals were necropsied and microscopically examined.

3.2. Sponsor's analysis

Survival analysis

The sponsor has applied log-rank test and trend analysis using ordinals (0, 1, 2, 3) and dose proportiomals (0, 1, 10, 20). The sponsor reported that there was no significant difference in mortality among treatment groups nor a significant dose-related trend in mortality. A summary of the survival distributions is given in Table 5.

Survival curves for male and female rats are shown in figures 3 and 4, respectively.

Tumor data analysis

The sponsor has applied similar methods of analysis as were described above in the mouse study. These tests were carried out for the incidence of tumors for Zaleplon doses versus the control. The results of analysis indicate that there was a significant positive dose-related trend in the number of animals with tumor for specific tumor types as shown in Table 6.

3.3. Reviewer's Analysis

Survival analysis

This reviewer has carried out a homogeneity analysis and a trend analysis on the survival data for male and female rats separately, using the statistical methods that were described above for the mouse study..

The results of analysis confirm the sponsor's results that there was no significant difference in mortality among treatment groups nor a significant dose-related trend in mortality.

Tumor data analysis

This reviewer has carried out the trend analysis for the tumor data, using the FDA's approach described above in the mouse study. The results of analysis for female and male rats are shown in Tables 7 and 8, respectively. Tables 7 and 8 show similar results as those found by the sponsor.

According to the FDA's rule stated above, none of the tumor types in both female and male rats are considered significantly dose-related.

4. SUMMARY AND CONCLUSION

This reviewer has carried out an analysis for survval and a trend analysis for the incidence of tumors, for both the mouse and the rat studies.

For the mouse study, the sponsor had studied 450 mice for each sex (75 mice for each of the groups receiving 0, 0 (two controls), 25, 50, 100 and 200 mg/kg/day) for carcinogenicity potential of Zaleplon. The results of the survival analysis showed that there is a statistically significant ($p\text{-value} \leq 0.04$) positive dose-related linear trend in mortality for both females and males. The results of analysis for the incidence of tumors show dose-related positive trend in liver adenoma,hepatocellular ($p\text{-value} < 0.001$) and in skin fibrosarcoma or sarcoma ($p\text{-value} = 0.02$) for female mice that is, in FDA's view, considered statistically significant.

For the rat study, the sponsor had studied 300 rats for each sex (120 rats for control and 60 rats for each of the groups receiving 1, 10, and 20 mg/kg/day) for carcinogenicity potential of Zaleplon. No significant results, in both the survival analysis and the tumor analysis, were found.

/S/ [redacted]

Walid A. Nuri, Ph.D.
Mathematical Statistician

This review consists of 5 ages, 8 tables, and 4 figures.

Concur: /S/ [redacted]
Dr. Jin
Dr. Chi

cc: HFD-120, orig. NDA 20-859
HFD-120/Dr. Atrakchi
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Dr. Nuri
Chron: W A Nuri: 594-5303 DB I: 10-16-98: DISC10/sonata.wpd

APPEARS THIS WAY ON ORIGINAL

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Table 1.

Sponsor's Survival Analysis for the Mouse Study (# 450)

	DOSAGE (mg/kg/day)				
	0	25	50	100	200
MALE					
Animals initially on study	150	75	75	75	75
Accidental deaths	0	0	0	0	0
Killed in extremis	5	0	0	1	0
Natural deaths	68	44	33	40	47
Animals surviving to study termination[a]	77	31	42	34	28
Kaplan-Meier endpoint survival rate (%)	51	41	56	45	37
Survival analysis (p-value)	0.04[b]				
FEMALE					
Animals initially on study	150	75	75	75	75
Accidental deaths	0	0	0	0	0
Killed in extremis	4	5	1	2	3
Natural deaths	81	41	41	48	53
Animals surviving to study termination[a]	65	29	33	25	19
Kaplan-Meier endpoint survival rate (%)	43	39	44	33	25
Survival analysis (p-value)	0.004[b]				

a: Based on number of mice surviving to scheduled sacrifice

b: Result of the trend test using dose proportional score.

Table 2. (Sponsor's Report)

Administered by Diet to Mice for Two Years (SN 450)

FEMALES

ORGAN	Dose Group: Combined Controls	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	Statistical Test	Trend p-value: Dose Scale	Trend p-value: Ordinal Scale
PITUITARY GLAND								
ADENOMA	1/148	3/73	2/73	2/74	0/72	Exact	.58	.41
SKIN								
CARCINOMA BASAL CELL	1/147	0/72	0/73	0/75	0/75	Exact	1.00	1.00
CARCINOMA BASOSQUAMOUS	1/147	0/72	0/73	0/75	0/75	Exact	1.00	1.00
FIBROSARCOMA	0/147	0/72	0/73	1/75	2/75	Exact	.01	.01
HEMANGIOMA	1/147	0/72	0/73	0/75	0/75	Exact	1.00	1.00
KERATOACANTHOMA	0/147	1/72	0/73	0/75	0/75	Exact	.67	.67
SARCOMA	0/147	1/72	0/73	0/75	0/75	Exact	.62	.62
FIBROSARCOMA OR SARCOMA	0/147	1/72	0/73	1/75	2/75	Exact	.02	.03
STOMACH								
CARCINOMA	1/148	0/73	0/73	0/73	0/72	Exact	1.00	1.00

Table 2 (cointinued)

Administered by Diet to Mice for Two Years (SN 450)

MALES

ORGAN	Dose Group					Statistical Test	Trend p-value	
	Combined Controls	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg		Dose Scale	Ordinal Scale
HARDERIAN GLANDS								
ADENOCARCINOMA	1/13	0/6	0/3	0/4	0/4	None	--	--
ADENOMA	2/13	2/6	0/3	1/4	0/4	None	--	--
HEART								
SARCOMA, NOS	0/150	0/74	0/75	1/75	0/75	Exact	.33	.33
HEMOLYMPHORET. SYS.								
HEMANGIOMA	2/150	0/75	1/75	0/75	0/75	Exact	.92	.92
HEMANGIOSARCOMA	2/150	0/75	0/75	1/75	0/75	Exact	.73	.80
HISTIOCYTIC SARCOMA	0/150	0/75	2/75	1/75	2/75	Exact	.06	.04
MALIGNANT LYMPHOMA	8/150	3/75	1/75	6/75	8/75	Peto	.02	.05
MYELOID LEUKEMIA	0/150	1/75	0/75	1/75	0/75	Exact	.43	.45
ILEUM								
ADENOCARCINOMA	1/123	0/60	0/62	0/58	0/58	Exact	1.00	1.00

Table 2 (cointinued)

Administered by Diet to Mice for Two Years (SN 450)

MALES

ORGAN	Dose Group					Statistical Test	Trend p-value	
	Combined Controls	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg		Dose Scale	Ordinal Scale
KIDNEYS								
ADENOMA,RENAL CELL	1/150	0/75	0/75	2/74	1/75	Exact	.13	.13
CARCINOMA,RENAL TUBULES	2/150	0/75	0/75	0/74	0/75	Exact	1.00	1.00
LIVER								
ADENOMA,HEPATOCELLULAR	25/147	6/75	10/74	10/75	13/75	Peto	.16	.29
CARCINOMA,HEPATOCELLULAR	10/147	5/75	5/74	5/75	5/75	Peto	.39	.40
HEMANGIOMA	1/147	0/75	1/74	0/75	0/75	Exact	.80	.80
LUNGS								
ADENOMA, BRONCHOALVEOLAR	44/150	21/75	16/74	20/75	16/75	Peto	.79	.83
CARCINOMA,BRONCHIOALVEOLAR	6/150	4/75	3/74	7/75	6/75	Peto	.04	.02
CARCINOMA,UNDIFFERENTIATED	1/150	0/75	0/74	0/75	0/75	Exact	1.00	1.00
ADENOMA OR CARCINOMA, BRONCHIOALVEOLAR	49/150	24/75	19/74	27/75	22/75	Peto	.33	.37

Table 2 (cointinued)

Administered by Diet to Mice for Two Years (SN 450)

FEMALES

ORGAN	Dose Group: Combined Controls	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg	Statistical Test	Trend p-value: Dose Scale	Trend p-value: Ordinal Scale
LIVER								
ADENOMA,HEPATOCELLULAR	2/149	3/75	1/73	4/75	9/75	Peto	<.001	<.001
CARCINOMA,HEPATOCELLULAR	0/149	0/75	1/73	1/75	0/75	Exact	.29	.20
LUNGS								
ADENOMA, BRONCHIOALVEOLAR	23/150	14/75	12/75	18/75	12/75	Peto	.18	.11
CARCINOMA,BRONCHIOALVEOLAR	8/150	1/75	0/75	4/75	4/75	Peto	.18	.33
HEMANGIOMA	0/150	0/75	0/75	1/75	1/75	Exact	.09	.09
ADENOMA OR CARCINOMA, BRONCHIOALVEOLAR	31/150	15/75	12/75	21/75	16/75	Peto	.11	.11
MAMMARY GLAND								
ADENOCARCINOMA	2/131	2/65	2/63	1/72	1/66	Exact	.50	.47
ADENOMA	1/131	0/65	0/63	0/72	0/66	Exact	1.00	1.00
FIBROADENOMA	1/131	0/65	0/63	0/72	0/66	Exact	1.00	1.00

Table 3. P-values for the tested tumor types for positive linear trend for female mouse. M=tumor is fatal to some animals, S=tumor is fatal to all animals. C=Control, L=Low, M=Medium, MH=Medium High, H=High dose of zaleplon. (Carried out by the reviewer).

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	MH	H
ADRENAL	ADENOMA,	S	0.6114	0.68070	0	1	0	0	0
ADRENAL	CARCINOM	S	0.4602	0.52210	0	1	0	1	0
ADRENAL	PHEOCHRO	M	0.3608	0.35335	0	0	1	2	0
BONE	OSTEOMA	S	0.5049	0.56390	0	0	1	0	0
BONE	OSTEOSAR	S	0.1529	0.02020	0	0	0	0	1
BRAIN	MENINGIO	S	0.1143	0.00915	0	0	0	0	1
BRAIN	OLIGODEN	S	0.5909	0.67485	0	1	0	0	0
DUODENUM	ADENOCAR	S	0.6344	0.69435	0	1	0	0	0
HARDERIA	ADENOCAR	S	0.6796	0.71885	0	1	1	0	0
HARDERIA	ADENOMA	S	0.3748	0.37670	0	0	1	1	0
HEMOLYMP	HEMANGIO	S	0.4207	0.43115	2	1	1	1	1
HEMOLYMP	HEMANGIO	S	0.7482	0.78040	0	2	1	0	0
HEMOLYMP	HISTIOCY	M	0.1556	0.15190	10	7	7	10	5
HEMOLYMP	MALIGNAN	M	0.3667	0.36995	25	16	19	12	11
KIDNEYS	CARCINOM	S	0.2571	0.21550	0	0	0	1	0
LIVER	ADENOMA,	M	0.0000	0.00000	2	3	1	4	9
LIVER	CARCINOM	S	0.2900	0.28780	0	0	1	1	0
LUNGS	ADENOMA,	S	0.1623	0.15965	23	14	12	18	12
LUNGS	CARCINOM	M	0.1166	0.10810	8	1	0	4	4
LUNGS	HEMANGIO	S	0.0956	0.05215	0	0	0	1	1
MAMMARY	ADENOCAR	S	0.2381	0.23195	2	2	2	1	1
MAMMARY	ADENOMA	S	1.0000	0.73895	1	0	0	0	0
MAMMARY	FIBROADE	S	1.0000	0.75280	1	0	0	0	0

Table 3 (continued)

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	MH	H
OVARIES	ADENOMA,	S	0.1143	0.00915	0	0	0	0	1
OVARIES	CYSTADEN	S	0.1267	0.10725	0	2	1	2	1
OVARIES	GRANULOS	S	0.2358	0.13200	1	0	0	0	1
OVARIES	SERTOLI	S	0.6114	0.68070	0	1	0	0	0
PANCREAS	ADENOMA	S	0.1650	0.02480	0	0	0	0	1
PARATHYR	ADENOMA	S	0.4457	0.49930	0	0	1	0	0
PITUITAR	ADENOMA	M	0.5722	0.59455	1	3	2	2	0
SKIN	CARCINOM	S	1.0000	0.77530	1	0	0	0	0
SKIN	CARCINOM	S	1.0000	0.78185	1	0	0	0	0
SKIN	FIBROSAR	S	0.0041	0.00030	0	0	0	1	2
SKIN	HEMANGIO	S	1.0000	0.75105	1	0	0	0	0
SKIN	KERATOAC	S	0.6518	0.70855	0	1	0	0	0
SKIN	SARCOMA	S	0.4933	0.60030	0	1	0	0	0
STOMACH	CARCINOM	S	1.0000	0.76755	1	0	0	0	0
TAIL	OSTEOSAR	S	1.0000	0.73645	0	1	0	0	0
THYROID	ADENOMA,	S	0.8631	0.86095	2	2	0	1	0
UTERUS	ADENOCAR	M	0.9233	0.89320	3	1	1	0	0
UTERUS	HEMANGIO	S	0.7724	0.78760	1	1	1	0	0
UTERUS	LEIOMYOM	S	0.4789	0.48595	4	2	1	1	2
UTERUS	LEIOMYOS	S	0.7780	0.78610	2	0	0	1	0
UTERUS	SARCOMA	S	1.0000	0.78485	1	0	0	0	0
UTERUS	SARCOMA,	S	0.1028	0.00590	0	0	0	0	1
VAGINA	ADENOMA,	S	0.1143	0.00915	0	0	0	0	1
VAGINA	MYXOMA	S	1.0000	0.76750	1	0	0	0	0

Table 4. P-values for the tested tumor types for positive linear trend for male mouse. M=tumor is fatal to some animals, S=tumor is fatal to all animals. C=Control, L=Low, M=Medium, MH=Medium High, H=High dose of zaleplon. (Carried out by the reviewer).

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	MH	H
ADRENAL	ADENOMA,	S	0.4158	0.42455	1	1	1	3	0
BONE	OSTEOSAR	S	1.0000	0.83775	1	0	0	0	0
EYES	FIBROSAR	S	1.0000	0.83775	1	0	0	0	0
HARDERIA	ADENOCAR	S	1.0000	0.80130	1	0	0	0	0
HARDERIA	ADENOMA	S	0.8363	0.83790	2	2	0	1	0
HEART	SARCOMA,	S	0.3361	0.29260	0	0	0	1	0
HEMOLYMP	HEMANGIO	S	0.8920	0.87460	2	0	1	0	0
HEMOLYMP	HEMANGIO	M	0.7235	0.72385	2	0	0	1	0
HEMOLYMP	HISTIOCY	M	0.0617	0.03725	0	0	2	1	2
HEMOLYMP	MALIGNAN	M	0.0181	0.01320	8	3	1	6	8
HEMOLYMP	MYELOID	S	0.4219	0.49375	0	1	0	1	0
ILEUM	ADENOCAR	S	1.0000	0.79875	1	0	0	0	0
KIDNEYS	ADENOMA,	S	0.1339	0.09355	1	0	0	2	1
KIDNEYS	CARCINOM	M	1.0000	0.88370	2	0	0	0	0
LIVER	ADENOMA,	M	0.1585	0.15560	25	6	10	10	13
LIVER	CARCINOM	M	0.3707	0.37550	10	5	5	5	5
LIVER	HEMANGIO	M	0.7763	0.79165	1	0	1	0	0
LUNGS	ADENOMA,	M	0.8009	0.79980	44	21	16	20	16
LUNGS	CARCINOM	M	0.0427	0.03585	6	4	3	7	6
LUNGS	CARCINOM	S	1.0000	0.80465	1	0	0	0	0
PANCREAS	CARCINOM	S	0.2381	0.04760	0	0	0	0	1
PROSTATE	ADENOCAR	S	1.0000	0.80130	1	0	0	0	0

Table 4 (continued)

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	MH	H
SEMINAL	ADENOMA	S	0.1349	0.01555	0	0	0	0	1
SEMINAL	LEIOMYOM	S	0.1463	0.11130	0	0	1	0	1
SKIN	HEMANGIO	S	1.0000	0.80430	1	0	0	0	0
SKIN	SARCOMA	S	0.1660	0.02470	0	0	0	0	1
TESTES	LEYDIG C	S	0.3269	0.32215	2	0	1	1	1
THYROID	ADENOMA,	S	1.0000	0.88485	2	0	0	0	0
URINARY	CARCINOM	S	1.0000	0.80285	1	0	0	0	0

Table 5.

Sponsor's Survival Analysis for the Rat Study (# 419)

GROUP	FEMALES	MALES
1: Control Diet	38/120[a] (32%)	53/120 (44%)
2: 1 mg/kg/day	23/60 (38%)	30/60 (50%)
3: 10 mg/kg/day	17/60 (28%)	30/60 (50%)
4: 20 mg/kg/day	23/60 (38%)	28/60 (47%)

a= denominator indicates initial group size.

There were no statistically significant differences in mortality among the dose groups nor a significant dose-related trend in mortality.

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Table 6. (Sponsor's Report)

Summary of Incidence and Trend Test Results for Primary Neoplasms
A Carcinogenicity Study with a Satellite PK/Hepatic Aspect of CL 284, 846 (Sedative/Hypnotic)
Administered by Diet to Rats (SN 419).

FEMALES

ORGAN	Dose Group				Statistical Test	Trend p-value	
	Control	1 mg/kg	10 mg/kg	20 mg/kg		Dose Scale 0, 1, 10, 20	Ordinal Scale 0, 1, 2, 3
BRAIN,CEREBRUM							
ASTROCYTOMA,MALIGNANT	0/119	0/60	1/60	0/60	Exact	.40	.40
HEART							
SCHWANNOMA,ENDOCARDIAL,FOCAL	0/120	1/60	0/60	0/60	Exact	.62	.62
HEMOLYMPHORET. SYS.							
HEMANGIOMA	0/120	1/60	0/60	0/60	Exact	.57	.57
HEMANGIOSARCOMA	1/120	0/60	0/60	0/60	Exact	1.00	1.00
HISTIOCYTIC SARCOMA	10/120	0/60	0/60	5/60	Peto	.42	.76
LYMPHOMA,MALIGNANT	0/120	0/60	1/60	2/60	Exact	.04	.04
MYELOID LEUKEMIA	1/120	1/60	0/60	0/60	Exact	.85	.85

Table 6 (cointinued)

Summary of Incidence and Trend Test Results for Primary Neoplasms
A Carcinogenicity Study with a Satellite PK/Hepatic Aspect of CL 284, 846 (Sedative/Hypnotic)
Administered by Diet to Rats (SN 419).

FEMALES

ORGAN	Dose Group				Statistical Test	Trend p-value	
	Control	1 mg/kg	10 mg/kg	20 mg/kg		Dose Scale 0, 1, 10, 20	Ordinal Scale 0, 1, 2, 3
PANCREAS							
ADENOMA,ISLET CELL,	1/120	3/60	0/60	0/60	Exact	.89	.86
CARCINOMA,ISLET CELL	1/120	2/60	1/60	0/60	Exact	.72	.67
PARATHYROID GLANDS							
ADENOMA	0/111	0/57	2/57	0/55	Exact	.44	.27
PITUITARY GLAND							
ADENOMA,PARS DISTALIS	80/118	43/59	51/60	44/60	Peto	.34	.30
CARCINOMA,PARS DISTALIS	2/118	2/59	4/60	6/60	Peto	.007	.007
ADENOMA OR CARCINOMA,PARS DISTALIS	82/118	45/59	55/60	50/60	Peto	.10	.08

Table 6 (cointinued)

Summary of Incidence and Trend Test Results for Primary Neoplasms
A Carcinogenicity Study with a Satellite PK/Hepatic Aspect of CL 284, 846 (Sedative/Hypnotic)
Administered by Diet to Rats (SN 419).

FEMALES

ORGAN	Dose Group				Statistical Test	Trend p-value	
	Control	1 mg/kg	10 mg/kg	20 mg/kg		Dose Scale 0, 1, 10, 20	Ordinal Scale 0, 1, 2, 3
SKIN							
CARCINOMA,BASAL CELL	0/119	0/58	0/60	2/60	Exact	.04	.04
CARCINOMA,SEBACEOUS	0/119	0/58	0/60	1/60	Exact	.20	.20
FIBROMA	1/119	2/58	1/60	1/60	Exact	.43	.42
FIBROSARCOMA	3/119	0/58	1/60	1/60	Exact	.58	.71
KERATOACANTHOMA	1/119	1/58	0/60	0/60	Exact	.85	.85
LIPOMA	4/119	1/58	0/60	1/60	Exact	.84	.91
THYMUS							
THYMOMA,BENIGN	2/99	4/53	0/52	0/52	Exact	.96	.92
THYMOMA,MALIGNANT	2/99	0/53	0/52	0/52	Exact	1.00	1.00
THYROID GLAND							
ADENOMA,FOLLICULAR	1/120	0/60	0/60	0/60	Exact	1.00	1.00
ADENOMA,PARAFOLLICULAR	6/120	2/60	6/60	3/60	Peto	.31	.31
CARCINOMA,PARAFOLLICULAR	0/120	0/60	0/60	2/60	Exact	.03	.03
ADENOMA OR CARCINOMA, PARAFOLLICULAR	6/120	2/60	6/60	5/60	Peto	.09	.11

Table 7. P-values for the tested tumor types for positive linear trend for female rat. M=tumor is fatal to some animals, S=tumor is fatal to all animals. C=Control, L=Low, M=Medium,H=High dose of zaleplon. (Carried out by the reviewer).

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ADIPOSE	LIPOMA	S	0.8899	0.86210	3	1	1	0
ADRENAL	ADENOMA	S	0.6386	0.72750	3	2	3	1
ADRENAL	CARCINOM	S	0.8493	0.87115	2	2	1	0
ADRENAL	PHEOCHRO	S	0.4244	0.34070	1	1	0	1
BRAIN,CE	ASTROCYT	S	0.4529	0.63010	0	0	1	0
HEART	SCHWANNO	S	0.6275	0.72180	0	1	0	0
HEMOLYMP	HEMANGIO	S	0.6212	0.67440	0	1	0	0
HEMOLYMP	HEMANGIO	S	1.0000	0.72985	1	0	0	0
HEMOLYMP	HISTIOCY	M	0.1390	0.09760	6	0	0	4
HEMOLYMP	LYMPHOMA	M	0.0457	0.03070	0	0	1	2
HEMOLYMP	MYELOID	S	0.7313	0.71265	0	1	0	0
ILEUM	ADENOCAR	S	1.0000	0.72215	1	0	0	0
KIDNEYS	ADENOMA,	S	0.4444	0.62905	0	0	1	0
LIVER	ADENOMA,	S	0.7466	0.61715	4	0	0	1
LIVER	CARCINOM	M	0.4658	0.56230	2	3	4	2
LUNGS	ADENOMA,	S	0.2353	0.03620	0	0	0	1
LYMPH N.	HEMANGIO	S	0.6212	0.67440	0	1	0	0
MAMMARY	ADENOCAR	S	.	.	10	11	10	9
MAMMARY	ADENOMA	S	0.6290	0.54500	1	3	1	1
MAMMARY	FIBROADE	S	.	.	10	31	14	12
OVARIES	ADENOCAR	S	0.4231	0.56675	0	0	1	0
OVARIES	GRANULOS	S	1.0000	0.72985	1	0	0	0
OVARIES	THECA/GR	S	0.3011	0.31780	1	0	1	1

Table 7 (continued)

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
PANCREAS	ADENOMA,	S	0.8951	0.88620	1	3	0	0
PANCREAS	CARCINOM	S	0.7123	0.80950	1	2	1	0
PARATHYR	ADENOMA	S	0.4434	0.70125	0	0	2	0
PITUITAR	ADENOMA,	M	.	.	55	43	51	43
PITUITAR	CARCINOM	M	0.0418	0.04455	2	2	4	5
SKIN	CARCINOM	S	0.0469	0.00400	0	0	0	2
SKIN	FIBROMA	S	0.7099	0.67070	0	2	1	0
SKIN	FIBROSAR	S	0.6933	0.73840	1	0	1	0
SKIN	KERATOAC	S	.	.	0	1	0	0
SKIN	LIPOMA	S	0.2083	0.02620	0	1	0	1
THYMUS	THYMOMA,	S	0.9574	0.91940	2	4	0	0
THYMUS	THYMOMA,	S	1.0000	0.72985	1	0	0	0
THYROID	ADENOMA,	S	1.0000	0.72985	1	0	0	0
THYROID	ADENOMA,	S	0.5410	0.60215	6	2	6	3
THYROID	CARCINOM	S	0.0353	0.00190	0	0	0	2
URINARY	POLYP,IN	S	0.2353	0.03620	0	0	0	1
UTERUS	ADENOMA,	S	0.6275	0.72180	0	1	0	0
UTERUS	LEIOMYOM	S	0.6212	0.67440	0	1	0	0
UTERUS	POLYP,EN	S	0.5607	0.50250	4	3	0	2
UTERUS	SCHWANNO	S	0.4391	0.69105	0	0	2	0
VAGINA	POLYP,ST	S	0.8093	0.78385	1	1	0	0

Table 8. P-values for the tested tumor types for positive linear trend for male rat. M=tumor is fatal to some animals, S=tumor is fatal to all animals. C=Control, L=Low, M=Medium,H=High dose of zaleplon. (Carried out by the reviewer).

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ADIPOSE	LIPOMA	S	0.8543	0.78470	1	1	0	0
ADRENAL	ADENOMA	S	0.7189	0.84890	0	3	2	0
ADRENAL	CARCINOM	S	1.0000	0.71580	1	0	0	0
ADRENAL	PHEOCHRO	S	0.4685	0.55285	4	1	5	2
ADRENAL	PHEOCHRO	S	0.3589	0.15530	1	0	0	1
BRAIN,CE	ASTROCYT	S	0.3968	0.10945	0	0	0	1
BRAIN,CE	ASTROCYT	S	0.1986	0.02280	0	0	0	1
BRAIN,CE	GRANULAR	S	0.6241	0.70700	0	1	0	0
BRAIN,CE	OLIGODEN	S	0.2654	0.04875	0	0	0	1
CECUM	CARCINOM	S	1.0000	0.80460	0	1	0	0
CECUM	NEUROFIB	S	1.0000	0.71580	1	0	0	0
COLON	LEIOMYOM	S	0.4114	0.62305	0	0	1	0
EYES	MELANOMA	S	0.6241	0.70700	0	1	0	0
HEART	MESOTHEL	S	0.1351	0.00605	0	0	0	1
HEART	SCHWANNO	S	1.0000	0.71580	1	0	0	0
HEMOLYMP	HEMANGIO	S	0.4114	0.62305	0	0	1	0
HEMOLYMP	HEMANGIO	S	1.0000	0.79090	2	0	0	0
HEMOLYMP	HISTIOCY	M	0.8054	0.76305	6	3	1	3
HEMOLYMP	LYMPHANG	S	1.0000	0.71580	1	0	0	0
HEMOLYMP	LYMPHOMA	M	0.9021	0.80650	1	1	0	0
HEMOLYMP	MYELOID	M	0.9319	0.88115	4	2	0	1
ILEUM	CARCINOI	S	0.1986	0.02280	0	0	0	1
ILEUM	NEUROFIB	S	0.6241	0.70700	0	1	0	0
KIDNEYS	CARCINOM	S	0.1217	0.13055	0	0	1	1

Table 8 (continued)

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
KIDNEYS	LIPOSARC	M	0.9733	0.83875	1	1	0	0
LIVER	ADENOMA,	M	0.4558	0.44790	2	3	1	2
LIVER	CARCINOM	M	0.8812	0.84615	9	2	2	2
LIVER	CHOLANGI	S	1.0000	0.71560	1	0	0	0
LUNGS	ADENOCAR	S	0.4114	0.62305	0	0	1	0
LUNGS	ADENOMA,	S	1.0000	0.72240	1	0	0	0
LUNGS	FIBROSAR	S	1.0000	0.72240	1	0	0	0
LYMPH N.	HEMANGIO	S	0.4114	0.62305	0	0	1	0
MAMMARY	FIBROADE	S	1.0000	0.79315	1	0	0	0
PANCREAS	ADENOCAR	S	0.6297	0.74015	1	0	1	0
PANCREAS	ADENOMA,	S	0.6927	0.79985	1	1	1	0
PANCREAS	ADENOMA,	S	0.2006	0.22320	9	4	8	7
PANCREAS	ADENOMA,	S	0.3589	0.15530	1	0	0	1
PANCREAS	CARCINOM	S	0.3750	0.45980	2	0	2	1
PARATHYR	ADENOMA	S	0.6552	0.73475	1	0	1	0
PITUITAR	ADENOMA,	M	0.9833	0.98245	60	31	38	30
PITUITAR	CARCINOM	S	1.0000	0.80235	0	1	0	0
SEMINAL	LEIOMYOS	S	0.6241	0.70700	0	1	0	0
SKEL.MUS	FIBROSAR	S	1.0000	0.71580	1	0	0	0
SKIN	ADENOMA,	S	0.5833	0.19930	0	0	0	1
SKIN	CARCINOM	S	0.4093	0.22755	1	0	0	2
SKIN	FIBROMA	S	0.8162	0.81185	0	4	1	2
SKIN	FIBROSAR	S	0.7715	0.75905	1	3	2	2
SKIN	KERATOAC	S	0.7231	0.79825	0	1	2	1
SKIN	LIPOMA	S	0.2308	0.25190	0	0	1	2
SKIN	MYXOSARC	S	0.8356	0.89595	0	1	1	0

Table 8 (continued)

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
KIN	SARCOMA,	S	0.5000	0.68270	0	0	1	0
SPLEEN	FIBROSAR	S	1.0000	0.71580	1	0	0	0
STOMACH,	CARCINOM	S	0.1986	0.02280	0	0	0	1
TESTES	LEYDIG C	S	0.0996	0.08880	3	2	2	4
THYMUS	THYMOMA,	M	0.5189	0.73665	0	0	2	0
THYROID	ADENOMA,	M	0.6061	0.65845	7	2	7	3
THYROID	ADENOMA,	S	0.4487	0.48725	10	6	9	6
THYROID	CARCINOM	S	0.0948	0.05770	1	0	1	2
THYROID	CARCINOM	S	1.0000	0.78995	2	0	0	0

Figure 1

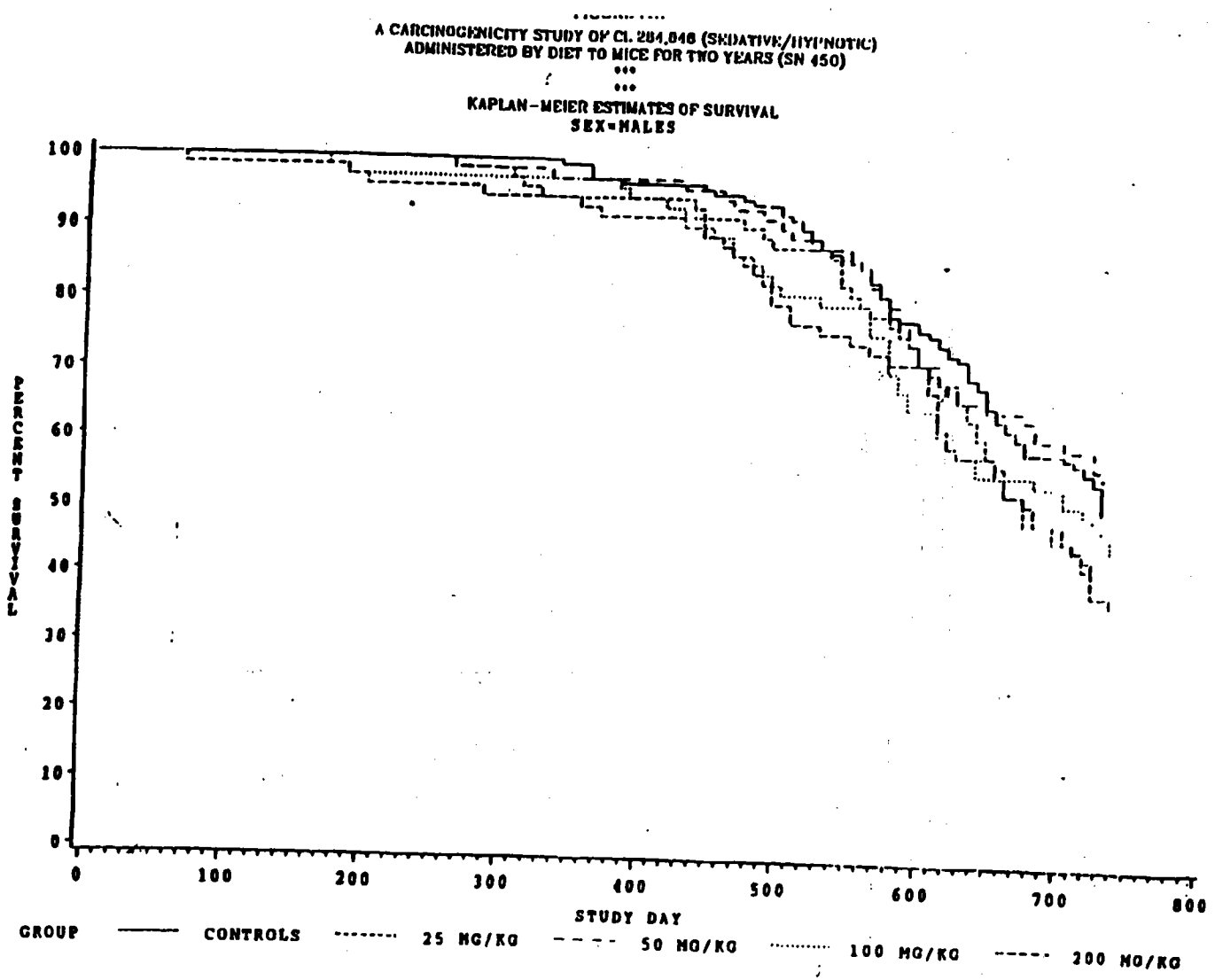
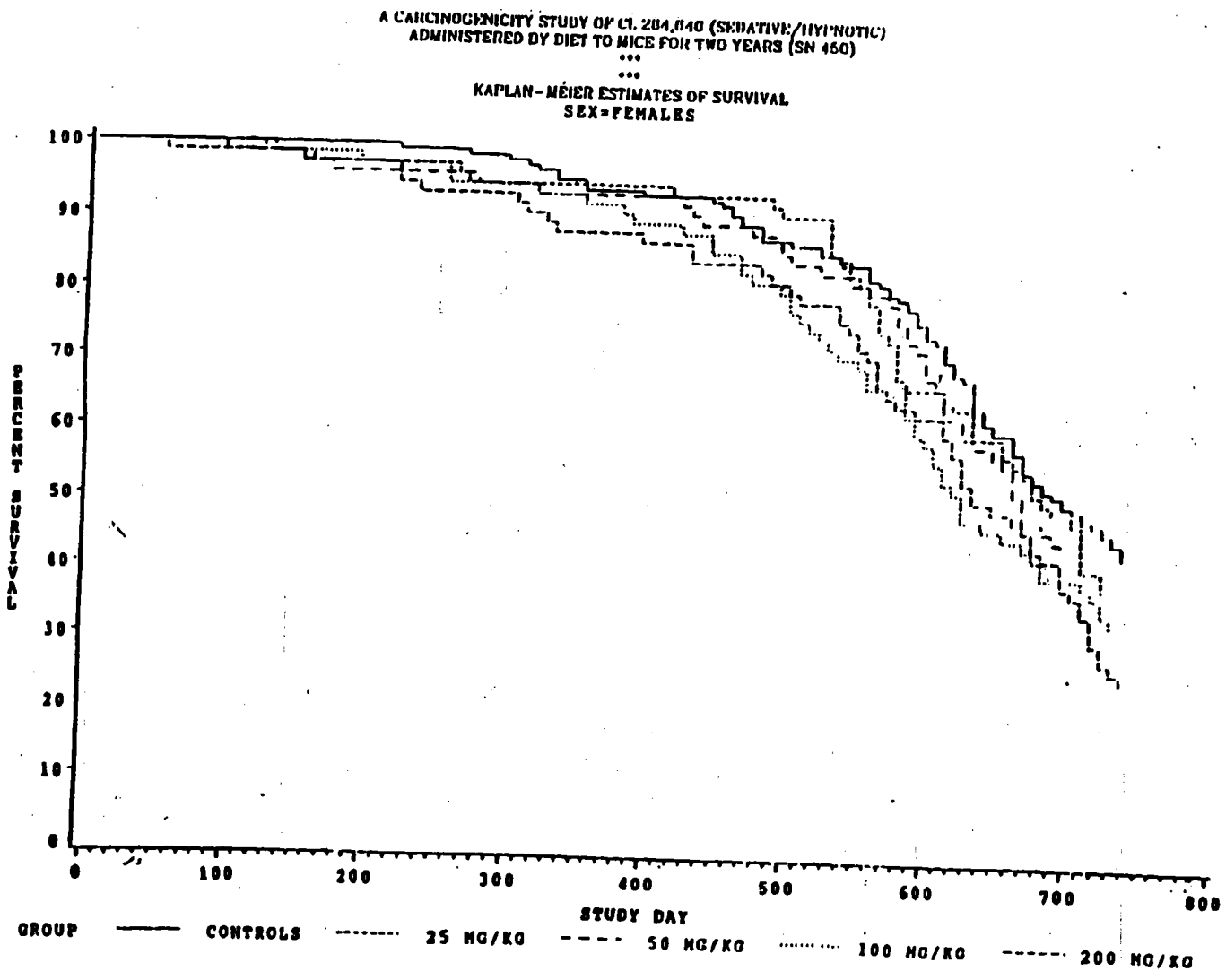

A CARCINOGENICITY STUDY OF CI. 284,046 (SEDATIVE/HYPNOTIC)
ADMINISTERED BY DIET TO MICE FOR TWO YEARS (SN 450)
KAPLAN-MEIER ESTIMATES OF SURVIVAL
SEX=MALES
PERCENT SURVIVAL
100
90
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
600
700
800
STUDY DAY
GROUP
CONTROLS
25 MG/KG
50 MG/KG
100 MG/KG
200 MG/KG

Figure 2


A CARCINOGENICITY STUDY OF CL 284,846 (SEDATIVE/HYPNOTIC)
ADMINISTERED BY DIET TO MICE FOR TWO YEARS (SN 460)
***
***
KAPLAN-MEIER ESTIMATES OF SURVIVAL
SEX=FEMALES
PERCENT SURVIVAL
100
90
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
600
700
800
STUDY DAY
GROUP
CONTROLS
25 MG/KG
50 MG/KG
100 MG/KG
200 MG/KG

Figure

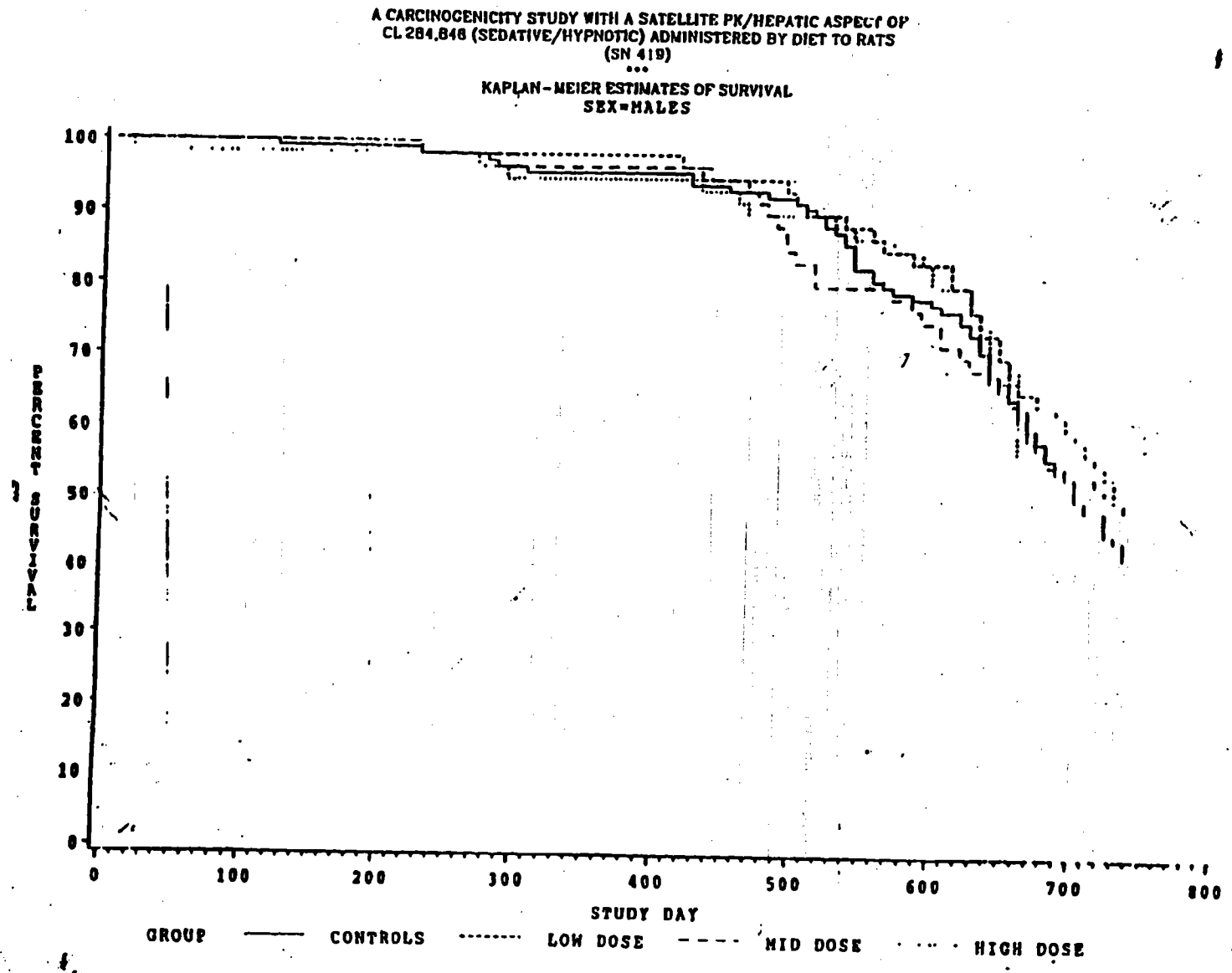

A CARCINOGENICITY STUDY WITH A SATELLITE PK/HEPATIC ASPECT OF
CL 284,846 (SEDATIVE/HYPNOTIC) ADMINISTERED BY DIET TO RATS
(SN 419)
...
KAPLAN-MEIER ESTIMATES OF SURVIVAL
SEX=MALES
PERCENT SURVIVAL
100
90
80
70
60
50
40
30
20
10
0
0
100
200
300
400
500
600
700
800
STUDY DAY
GROUP
CONTROLS
LOW DOSE
MID DOSE
HIGH DOSE

Figure 4

A CARCINOGENICITY STUDY WITH A SATELLITE PK/HEPATIC ASPECT OF CL 284,846 (SEDATIVE/HYPNOTIC) ADMINISTERED BY DIET TO RATS (SN 419)

KAPLAN-MEIER ESTIMATES OF SURVIVAL
SEX=FEMALES