HFD-120
Original

Statistical Review and Evaluation

DATE: MAR 31 1994

IND#:

APPLICANT: R. W. Johnson

NAME OF DRUG: Topimax, (topiramate)

DOCUMENTS REVIEWED: Sixteen Volumes Dated Dec. 01, 1992, Aug. 27 1993, and Dec. 08, 1993.

I. Background

The above submissions contain the data and results of the two carcinogenicity studies in rodents: a two-year study in rats and a 93/94-week study in mice. The data were also submitted on diskettes.

II. The Rat Study

II.a. Design

This study was conducted in Crl:(WI)BR,VAF/Plus rats at Charles River, NY. Fifty animals per sex were assigned to two control groups, and to each of the low, mid and high dose groups. The controls received diet only, the actively treated animals received 20 mg/kg, 45 mg/kg, and 120 mg/kg/day as dietary admixture. Water was available ad lib. Data from control group I were used in the assessment of mortality and of gastrin levels. Control group II was used in the assessment of mortality and of the tumorigenic potential of the drug. Animals found moribund or dead and all animals surviving to terminal sacrifice were sacrificed, necropsied, and histopathologically examined.

Survival data were analyzed by the regression model/life table method of Cox, and the generalized Kruskal-Wallis method of Gehan and Breslow. Incidental tumors were analyzed using Peto's prevalence method using the ad hoc selection of time intervals. Fatal tumors were analyzed by Peto's death rate method and fatal and incidental tumors of the same kind were appropriately combined. Mortality independent tumors were analyzed with Peto's onset-rate method.

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

Survival Analysis: Survival data were analyzed per sex treating the animals sacrificed at the end of the study as censored. Both the Cox and Gehan-Breslow tests indicated a statistically significant ($p<.05$) increasing trend with dose for male rats. The survival pattern of the female rats did not distinguish between the treatment groups.

Tumor Data Analysis: Peto's prevalence method did not show any dose related increases for either males or females in incidental or possibly incidental tumors. Similarly, there was no statistically significant dose related increase associated with fatal or possibly fatal tumors. The combining of incidental and fatal tumors of the same type did not result in a statistically significant finding. There were also no statistically singificant dose related increases in mortality-independent tumors for either male or female rats. The sponsor noted, however, a decrease in the incidence of non-fatal and malignant mammary gland tumors in female rats of all topiramate-treated groups when compared to their controls.

II.c. Reviewer's Analyses

Survival Analysis: The intercurrent mortality rates for both the male and female rats are given in Table 1. Of the male rats 22, 31, 35, and 35 animals respectively survived until the terminal sacrifice from control II, and the low, mid, and high dose groups. The corresponding survival till the end of study for the female rats was 29, 32, 22, 28 animals respectively. As the sponsor noted, the female rat groups were not statistically differentiable in their survival experience (Table 2, Figs. 1 and 2). For the male rats, however, both the Cox method and the generalized Kruskal Wallis analysis showed significant ($p \leq .05$) differences in the survival curves. The pairwise comparisons showed that the survival experience of the control rats was worst. The difference of the control group from the low treatment group was barely statistically significant ($.03 \leq p \leq .06$, depending on type of test). The remaining comparisons of the control group with the medium and high dose groups were significant at $p \leq .01$. The treated groups did not differ significantly from each other in survival. These results are consistent with the sponsor's.

Tumor Data Analysis: This reviewer also analyzed the tumor data independently. Tumor types with possible positive linear trend were generally analyzed by an exact permutation trend test (an approximate permutation trend test was used when fatal and incidental tumors of the same kind had overlapping time intervals). All tests are survival adjusted. Treatment groups are weighted by the actual dose levels, i.e. 0 (control group II), 20, 45, 120 mg/kg. Tumors with < 1.00 % of occurrence in the control group are considered rare and a trend test is statistically significant when it reaches a p-value of $\leq .05$. Higher tumor occurrences in the control group are considered common for these animals and a trend is statistically significant when its p-value is less than .01.

Like the sponsor, this reviewer did not observed a significant positive linear trend for any of the listed tumor findings (therefore there is no Tumor Table for rats).

Of note, however, is the fairly frequent occurrence of tumors labeled as "EXCL" and as "AUTO". In checking with the sponsor it was confirmed that these labels represent tissues excluded or autolyzed. The male rats had 401 tumor tissues recorded. Of these 148 (36.9 %) were classified as excluded or autolyzed. For the female rats there were 399 tumor tissues recorded. Of these 94 (23.6 %) were classified as excluded or autolyzed. Had these tissues shown any tumors it could have been possible to observed significant trends in tumor incidences.

II.d. Validity of the Rat Study

In the rat study there were no significant positive linear trends with dose in tumor incidence rates. However, before concluding that the rat study showed no tumorigenic effect of topiramate, 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, pp385-392, 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 suugested 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 Bioassay, 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 an indication that the treatment has been tested on levels at or approaching the MTD."

The sponsor stated that the upper dose was specifically selected as the estimated MTD derived in a 12-months toxicity study. In addition, the sponsor observed treatment-related non-neoplastic changes in the stomach of male and female rats of the 45 and 120 mg/kg dosages, in the liver of both sexes of all compound-treated groups, and in the kidneys of male rats at the 120 mg/kg/day and female rats of all dosage groups. In general, the incidence and/or severity of the changes in these tissues occurred in a dose-related manner.

The body weight means of the 20, 45, and 120 mg/kg males and females were lower ($p \leq .05$) than their respective controls. Male body weight means were lower from approximately month 3 to month 5 at 20 mg/kg, from approximately month 3 to month 12 at 45 mg/kg, and throughout most of the study at 120 mg/kg. The maximum difference from control ranged from 4% at 20, 4,5% at 45, to 8% at 120 mg/kg. Female body weight means were lower from the 4th month through most of the remainder of the study for the low treament group, and throughout most of the study at the mid and high doses. The maximum differences from control were 8% at 20, 12% at 45, and 23% at 120 mg/kg.

In addition, the survival of all treated rats was over 50 % at the end of two years.

Based on all these findings, this reviewer concludes that the animals in this rat study were dosed at a sufficiently high dose and for a sufficient length of time that late developing tumors

could have developed. It needs to be assessed, however, whether the proportions of unusable tissues are too great and cast doubt on the findings and conclusions based on the usuable tissues.

III. The Mouse Study

III.a. Design

This study was conducted in 700 CRL:CD-1(ICR)BR,VAF/Plus mice from Charles River Kingston, NY. (The sponsor noted that the designation of strain CRL:COBS CD-1(ICR)BR written in the protocol and raw data is incorrect).

There were two control groups per sex receiving diet only. The treated animals were dosed at 20, 75, and 300 mg/kg/day in oral/dietary admixture. Water was available ad lib. The selection of the high does was based on the estimated MTD from a 6-month dose-range study. The low dosage represents the estimated average daily human therapeutic dose, and the mid dose is approximately halfway between the low and high dosages on a log scale. The male mice were dosed at 100 - 105 % of their target doses. The female mice received 110 - 125 % of their target doses.

Control group I mice had only their urinary bladders examined for tumors because of the findings at the end of the study (tissues of control group I had been fixed in formalin), i.e. control group I entered into the statistical evaluation of survival and of urinary bladder tumors only.

At week 53 of the study 10 mice per sex per dose were sacrificed and necropsied. These data were not submitted on diskette.

One animal each of the male control groups had to be returned to the supplier. Otherwise, 60 animals per treatment group were studied for 93-94 weeks. In all analyses but those involving urinary bladder tissues, control group II was the reference group.

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

Survival Analysis: Survival data were analyzed per sex, treating the animals sacrificed at the end of the study as censored. The sponsor again used the Cox and the Gehan-Breslow methods for testing homogeneity and linear trend in survival curves. Neither with group II alone nor with the combined control groups did the sponsor find any statistically significant differences in survival.

Tumor Data Analysis: The sponsor applied the same statistical methodologies to the mice data as he did to the rat data. The time intervals were again obtained by Peto's ad hoc method.

Using only control group II, the sponsor observed statistically significant increases in mortality adjusted incidence rates with increasing dose for non-fatal urinary bladder leiomyosarcoma in males and in females, and for non-fatal urinary bladder tumors and for malignant urinary bladder tumors in females. When the two control groups were combined, non-fatal urinary bladder leiomyosarcoma in males and in females as well as urinary bladder tumors and malignant urinary bladder tumors in females showed again statistically significant increased (mortality adjusted) incidence rates with increasing dose. Fatal urinary bladder leiomyosarcoma in males showed also a significant increase with dose. Most of these tumor findings remained significant when incidental and fatal kinds were combined.

The sponsor also listed a series of statistically significant findings when there was only a single occurrence in the high-dose group (pp. 06 00142 ff, Vol.6/15): fatal meningioma in males, fatal kidney tubular carcinoma in males, skin undifferentiated sarcoma or hemangioma of skin in males, lymphoreticular system thymic lymphosarcoma in females, mediastinum ostergenic sarcoma in females, ovaries hemangioma in females, skin schwannoma in females, and uterus schwannoma in females. In addition the following tumors had statistically significant tumor findings, though with "low" incidence rates: lung bronchiolo-alveolar carcinoma in females and uterus endometrial polyp in females.

For the animals of the 1-year interim sacrifice several histopathological observations reached statistical significance over the control data. In the male mice they were (cf. pp. 06 0035 ff, Vol. 6/15) mixed inflammatory cell infiltration of the trachea, similar inflammatory cell infiltration of the lung, central hepatocellular hypertrophy, midzanal hepatocellular hypertrophy, and degenerative luminal cell of the epididymis. In the female mice the following tumors reached statistical significance when a treated group was compared with the control group: reticuloendothelial cell hyperplasia of the mandibular lymph node, dilated gastric fundic glands and lympocytic infiltrations of the stomach, amyloidosis of the stomach mucosa, tubular dilation of the kidneys, cortical amyloidosis of the adrenal glands, and dilation of the harderian gland.

III.c. Reviewer's Analyses

Survival Analysis: Ten animals per sex and dose group were sacrificed after one year. These animals were not included on the diskette and are not part of the survival analysis.

The intercurrent mortality rates for both the male and female mice intended for the whole study are given in Table 3. Among the male mice 41, 44, 40, 53, and 47 % survived until terminal sacrifice from the control I, control II, low, mid, and high dose groups respectively. The corresponding survival rates till the

end of study for the female mice were 48, 30, 40, 37, and 27 %. This reviewer included the two control groups as separate groups in the analyses. Neither the Cox statistic nor the Gehan-Breslow tests showed significant heterogeneity of survival curves nor a significant trend with increasing dose for either the male or female mice (Table 4, Figs. 3 and 4). These findings are consistent with the sponsor's. The only significant finding ($p<.02$) was a pairwise comparison of the female control group I and their high dose group, the high dose group having the poorer survival.

Tumor Data Analysis: The sponsor's control group I, II, low, medium and high dose groups were labeled groups 0, 1, 2, 3, 5 respectively on the diskettes.

Tumor types with 10 or less occurrences across treatment groups are generally analyzed by an exact permutation trend test. Occasionally an approximate permutation trend test was used when tumor occurrences of the fatal and non-fatal kind fell into the same time interval upon combination. Treatment groups are weighted by the actual dose levels, i.e. 0 (control group II), 20, 75, and 300 mg/kg. Tumors with < 1.00 % of occurrence in the control group are considered rare and a trend test is statistically significant when it reaches a p-value of $\leq .05$. Higher tumor occurrences in the control group are considered common for these animals and a trend is statistically significant when its p-value is less than .01.

The sponsor should have included the tumor findings of the interim-sacrificed animals on the diskette so that they could be integrated in the analyses of incidental tumors. As a second best, this reviewer used the hard copy data and applied the trend test to the significant tumor findings reported by the sponsor. These findings and those of the sponsor's are listed in Table 5. Most of the tumors which by the sponsor's Fisher's Exact test had significant findings did not remain statistically significant under the exact permutation trend test, because typically the high dose group did not have frequent tumor occurrences. This reviewer did not undertake to combine the findings of the interim sacrifice (hard copy) with those of the incidental tumors of the whole study. It is possible, that some tumors which showed no significant linear trend in either the interim sacrifice data nor in the data of the whole study could have exhibited a positive linear trend had the data been analyzed together.

The tumor analyses of the 60 remaining animals per group follow. The sponsor used different time intervals than this reviewer. This may affect some numeric results but none of the conclusions. Tumor incidences with possible positive trends with increasing dose were analyzed. For the male mice leiomyosarcoma of the urinary bladder showed a significant positive trend for "unrecorded" cause at p=.05. When the "unrecorded" cause is

combined with the "undetermined" cause, the p-value reaches .0138, just at the critical level for a common tumor (Table 6). This reviewer did not find a fatal leiomyosarcoma of the urinary bladder listed for male mice. Among female mice, leiomyoma of the cervix, cause "unrecorded", showed a statistically significant positive trend at p=.04. When combining these findings with "non-fatal" leiomyoma (i.e. all non-fatal tumors) the trend is no longer significant (p=.09). "Non-fatal" leiomyosarcoma of the urinary bladder in the females showed a highly signficant positive trend (p=.0003), which was maintained when combined with "unrecorded" and "undetermined" causes (p=.006). The single fatal leiomysarcoma of the urinary bladder in females did not reach statistical significance. When leiomyosarcomas of all causes were combined the linear positive trend was significant at p=.008. There were other tumors of the urinary bladder observed for female mice. They were of differing kinds and did not individually show statistically significant trends. This reviewer did not combine them as the sponsor did.

The sponsor also listed several tumors with a single occurrence in the high dose groups or others with "low" incidence rates as statistically significant findings. By any standard statistical test, a sample size of 60 per group is insufficient to reach statistical significance at the p=.05 level when there is only one occurrence of a tumor, albeit in the high dose group. This reviewer found that with sample size of 70 per group (which would be the wrong sample size because the data of the interim sacrifice were not included in the tumor analyses), the assymptotic trend test is significant at the p=.05 level (which would be the wrong test to use because the number of tumor occurrences is very small). If very rare, the tumors with a single occurrence in the high dose groups may be of clinical importance, but this study is not powerful enough to show these occurrences as statistically significant. This reviewer also tested for positive linear trend in the tumors listed as having "low" incidence rates by the sponsor. None reached statistical significance.

Of note, however, is the frequent occurrence of tumors labeled as "EXCL" and as "AUTO". The male mice had 550 tumor tissues recorded. Of these 408 (74.2 %) were classified as excluded or autolyzed. The most startling example is with mammary gland tissues of the male mouse, where 188 tissues are recorded as having been excluded and no other findings are reported for this organ. For the female mice there were 444 tumor tissues recorded. Of these 285 (64.2 %) were classified as excluded or autolyzed. It is clear, that had these tissues shown any tumors, many possible positive trends in tumor incidences could have been observed. It needs to be determined whether the small subset of usuable tissues gives a sufficient picture of the potential oncogenic activity of this product.

IV. Summary

The rat study showed some statistically significant difference in survival among the male animals. However, the survival for the control groups was worse than that of the topiramate treated groups. No statistically significant positive linear trends (linear component of the treatment effect) in the tumor incidence rates were observed. The validity of the study held with regard to assessing the number of animals exposed to a sufficient length of time at a sufficiently high dose.

The mouse study showed no significant heterogeneity or positive linear trend in survival patterns. However, there were significant (survival adjusted) positive trends in the tumor incidence rates of leiomyosarcoma of the urinary bladder in both males and females. Also, incidence rates from the interim sacrifice alone manifested statistically significant positive linear trends for central hepatocellular hypertrophy in male mice, lymphocytic infiltrations of the stomach in female mice, and tubular dilations of the kidneys in female mice. Some other low occurring tumors did not reach statistical significance in this reviewer's analyses though the sponsor had reported them as statistically significant findings.

Both studies, but expecially the mouse study, had large percentages of the organ tissues (24-74 %) reported as excluded or autolyzed. The above evaluations are, of course, based on the findings of the usable tissues. If the unusable tissues contained tumors it is statistically possible that linear positive trends in tumor incidence rates with increasing dose could have been observed, even in the rat study.

Roswitha Kelly
Roswitha E. Kelly
Mathematical Statistician

Concur:

Karl K. Lin 3/31/94
Karl K. Lin, Ph. D.
Group III Leader

cc:HFD-120/Original IND (No Attachments)
HFD-120/Dr. Fisher (No Attachments)
HFD-710/Chron. (No Attachments)
HFD-715/Chron. (No Attachments)
HFD-715/Dr. Lin (No Attachments)
HFD-715/Ms. Kelly (Attachments)
HFD-715/DRU 2.1.1 Topimax, R. W. Johnson (Attachments)
HFD-715/RKELLY/02/03/94/wp-ind28549.rev

Table 1
INTERCURRENT MORTALITY RATES
RAT STUDY

Sex	Time (wks.)	Control II	mg/kg/day 20	45	120
MALES	0 - 52	4/50 (8%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
	53 - 78	6/46 (20%)	5/49 (12%)	8/50 (16%)	3/49 (8%)
	79 - 92	12/40 (44%)	5/44 (22%)	0/42 (16%)	3/46 (14%)
	93 -104	6/28 (56%)	8/39 (38%)	7/42 (30%)	8/43 (30%)
	Term. Sacr.	22/50 (44%)	31/50 (62%)	35/50 (70%)	35/50 (70%)
FEMALES	0 - 52	1/50 (2%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
	53 - 78	6/49 (14%)	3/49 (8%)	5/50 (10%)	1/50 (2%)
	79 - 92	7/43 (28%)	9/46 (26%)	5/45 (20%)	11/49 (24%)
	93 -104	7/36 (42%)	5/37 (36%)	7/40 (34%)	10/38 (44%)
	Term. Sacr.	29/50 (58%)	32/50 (64%)	33/50 (66%)	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 2
Results of Intercurrent Mortality Analyes
Rat Study

Sex	Groups Compared	Direction	Two-tailed P-Value of Test Cox	Kruskal/Wallis
MALES	C,L,M,H	neg	.017	.013
	C,L	neg	.062	.030
	C,M	neg	.010	.007
	C,H	neg	.007	.003
	L,M	neg	.498	.434
	L,H	neg	.476	.366
	M,H	pos	.962	.958
FEMALES	C,L,M,H	pos	.816	.980
	C,L	neg	.645	.537
	C,M	neg	.452	.334
	C,H	pos	.941	.738
	L,M	neg	.924	.760
	L,H	pos	.659	.707
	M,H	pos	.444	.425

Interpretation of Direction of Trend: Trend is labeled positive when survival is poorer (i.e. mortality is greater) in the comparison (right-hand) group than in the reference (left-hand) group; the trend is labeled negative when survival is better in the comparison group than in the reference group.

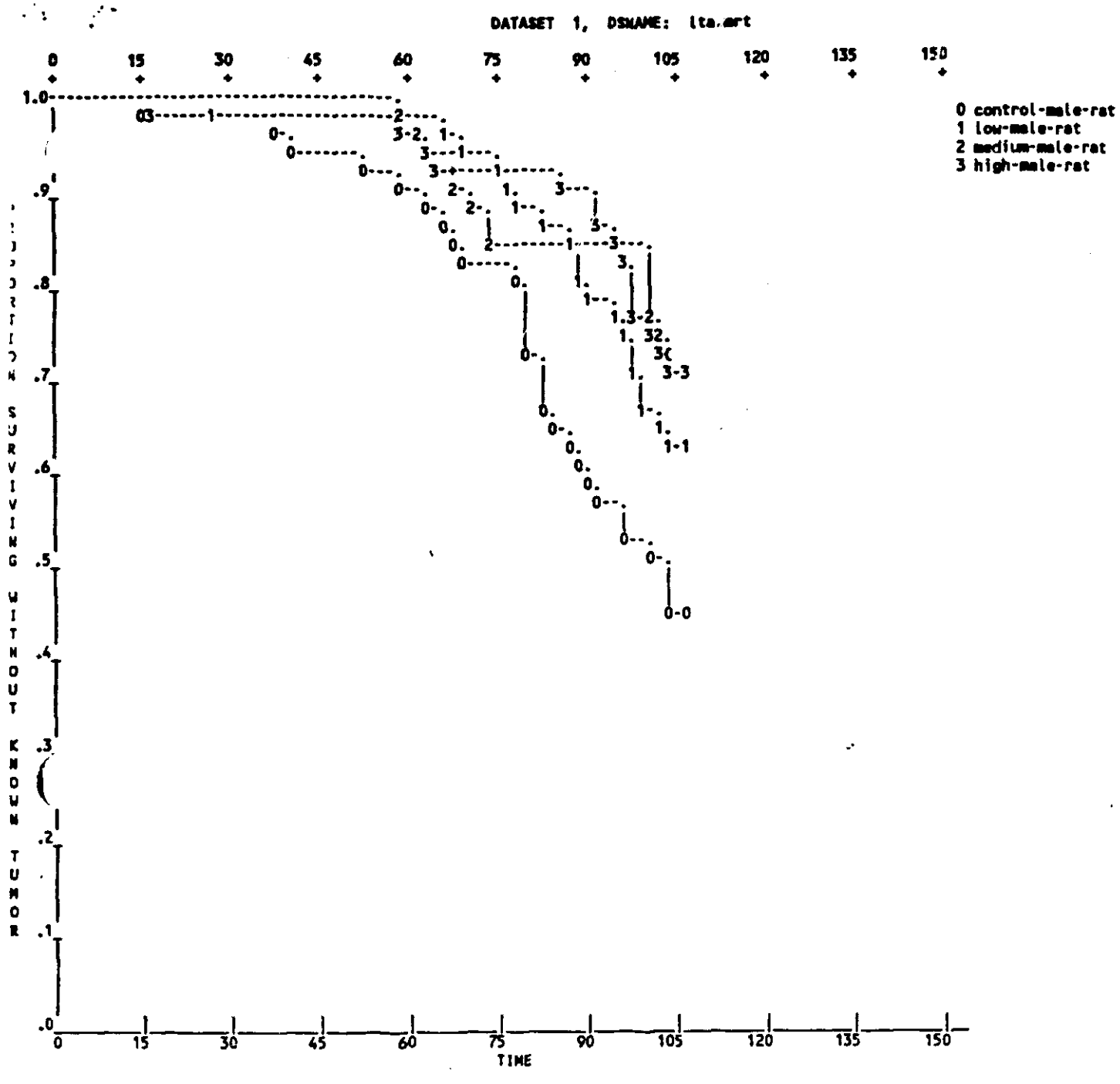

Figure 1: Male Rat Survival Curves

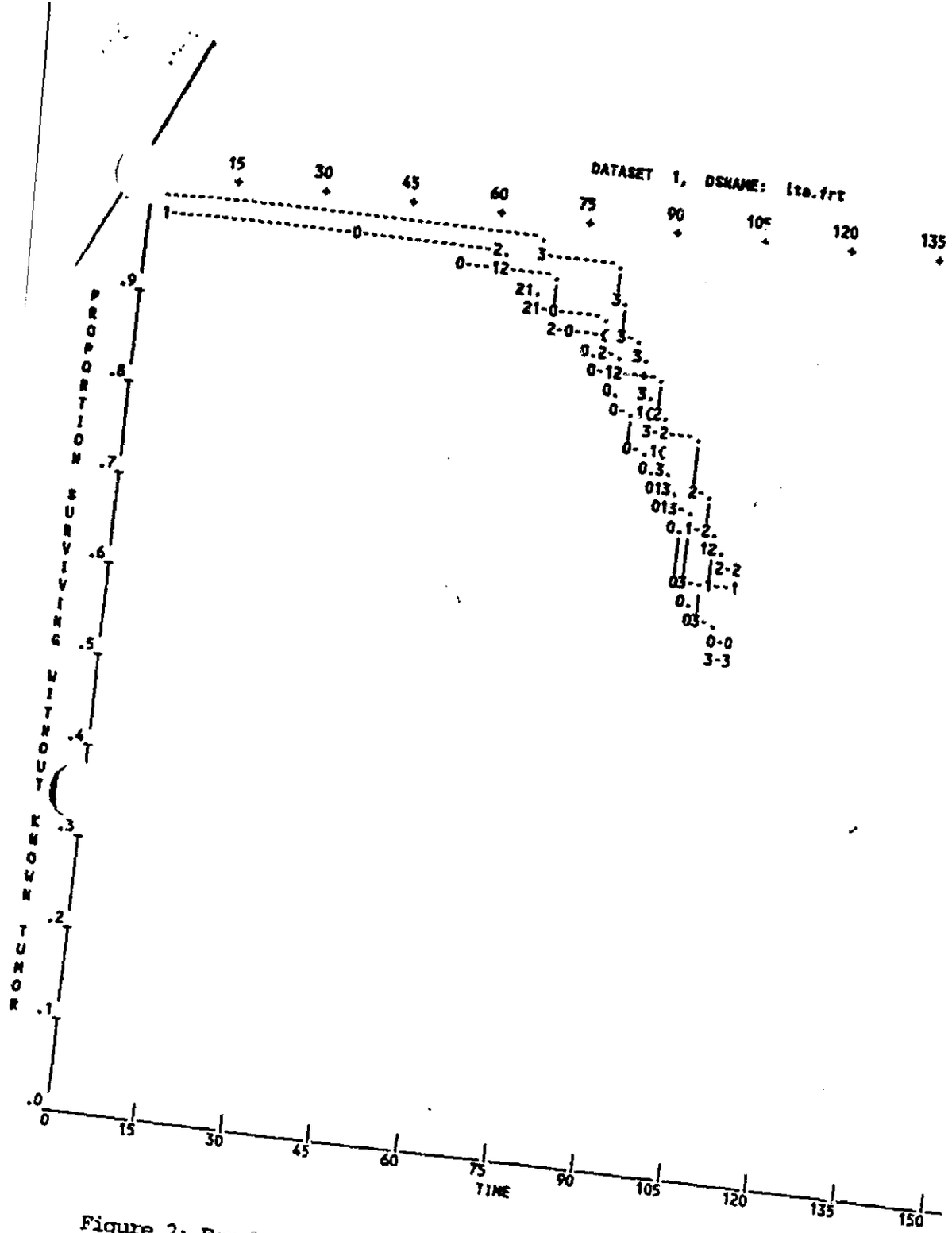

Figure 2: Female Rat Survival Curves

Table 3
INTERCURRENT MORTALITY RATES
MOUSE STUDY

Sex	Time (wks.)	Cntrl I	Cntrl II	mg/kg/day		
		0	0	20	75	300
MALES	0-52	3/59 (5%)	4/59 (7%)	3/60 (5%)	2/60 (3%)	8/60 (13%)
	53-78	13/56 (27%)	15/55 (32%)	13/57 (27%)	14/58 (27%)	11/52 (32%)
	79-93	19/43 (59%)	14/40 (56%)	20/44 (60%)	12/44 (47%)	13/41 (53%)
	T.S.	24/59 (41%)	26/59 (44%)	24/60 (40%)	32/60 (53%)	28/60 (47%)
FEMALES	0-52	3/60 (5%)	4/60 (12%)	1/60 (2%)	1/60 (2%)	3/60 (5%)
	53-78	13/57 (27%)	22/56 (43%)	20/59 (35%)	18/59 (32%)	22/57 (42%)
	79-93	15/44 (52%)	16/34 (70%)	15/39 (60%)	19/41 (63%)	19/35 (72%)
	T.S.	29/60 (48%)	18/60 (30%)	24/60 (40%)	22/60 (37%)	16/60 (27%)

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 parenthesis for this row represents the number of animals surviving to terminal sacrifice.

Table 4
Results of Intercurrent Mortality Analyes
The Mouse Study

Sex	Groups Compared	Direction	Two-tailed P-Value of Test Cox	Kruskal/Wallis
MALES	C1,C1,L,M,H	neg	.704	.898
	C1,C2	pos	.916	.912
	C1,L	pos	.956	.981
	C1,M	neg	.317	.370
	C1,H	neg	.813	.939
	C2,L	pos	.970	.942
	C2,M	neg	.396	.348
	C2,H	neg	.918	.881
	L,M	neg	.294	.358
	L,H	neg	.764	.899
	M,H	pos	.529	.422
FEMALES	C1,C1,L,M,H	pos	.057	.070
	C1,C2	pos	.068	.071
	C1,L	pos	.364	.319
	C1,M	pos	.270	.299
	C1,H	pos	.019	.021
	C2,L	neg	.416	.367
	C2,M	neg	.547	.392
	C2,H	pos	.651	.593
	L,M	pos	.914	.922
	L,H	pos	.188	.167
	M,H	pos	.236	.147

Interpretation of Direction of Trend: Trend is labeled positive when survival is poorer (i.e. mortality is greater) in the comparison (right-hand) group than in the reference (left-hand) group; the trend is labeled negative when survival is better in the comparison group than in the reference group.

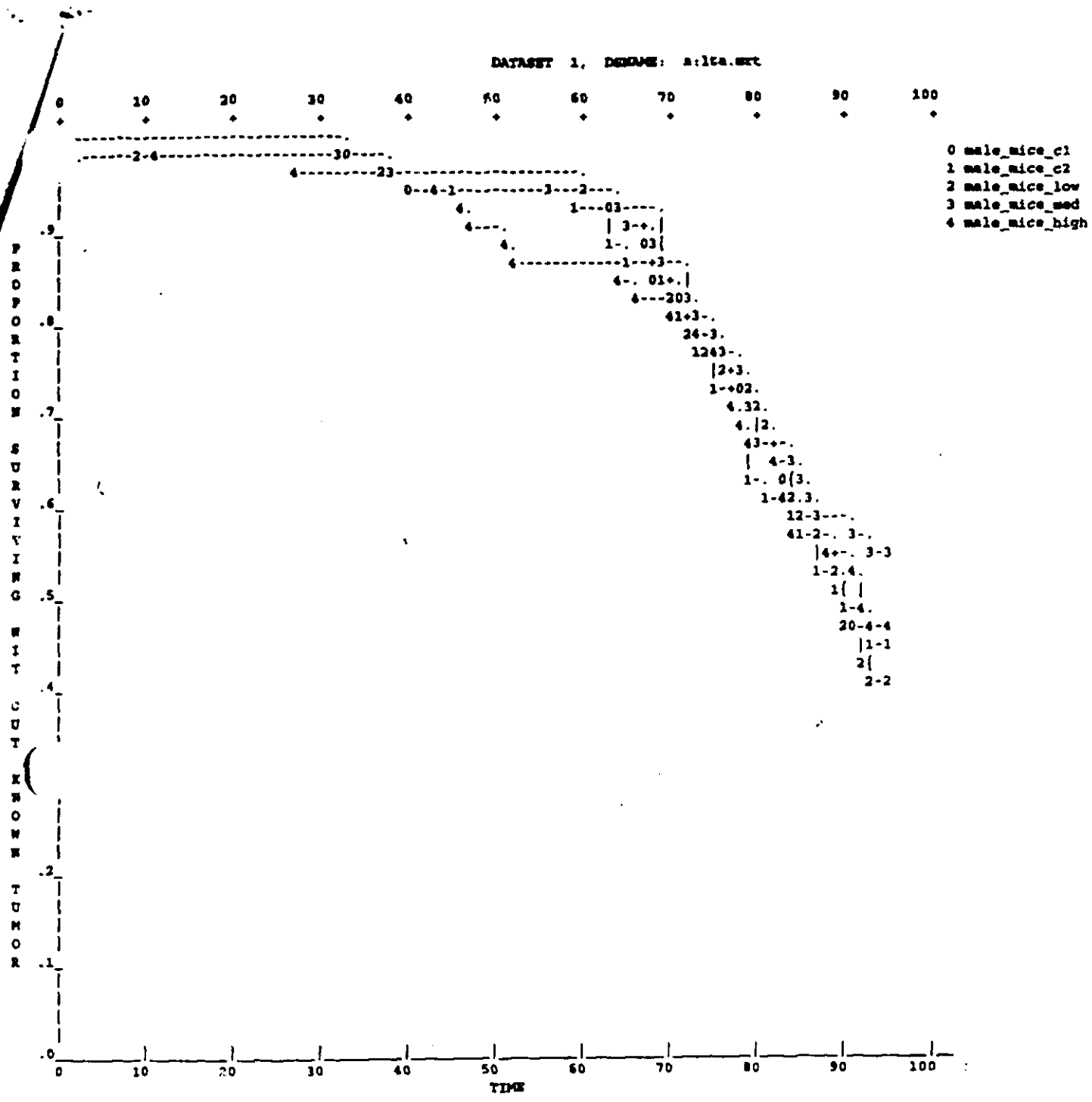

Figure 3: Male Mice Survival Curves

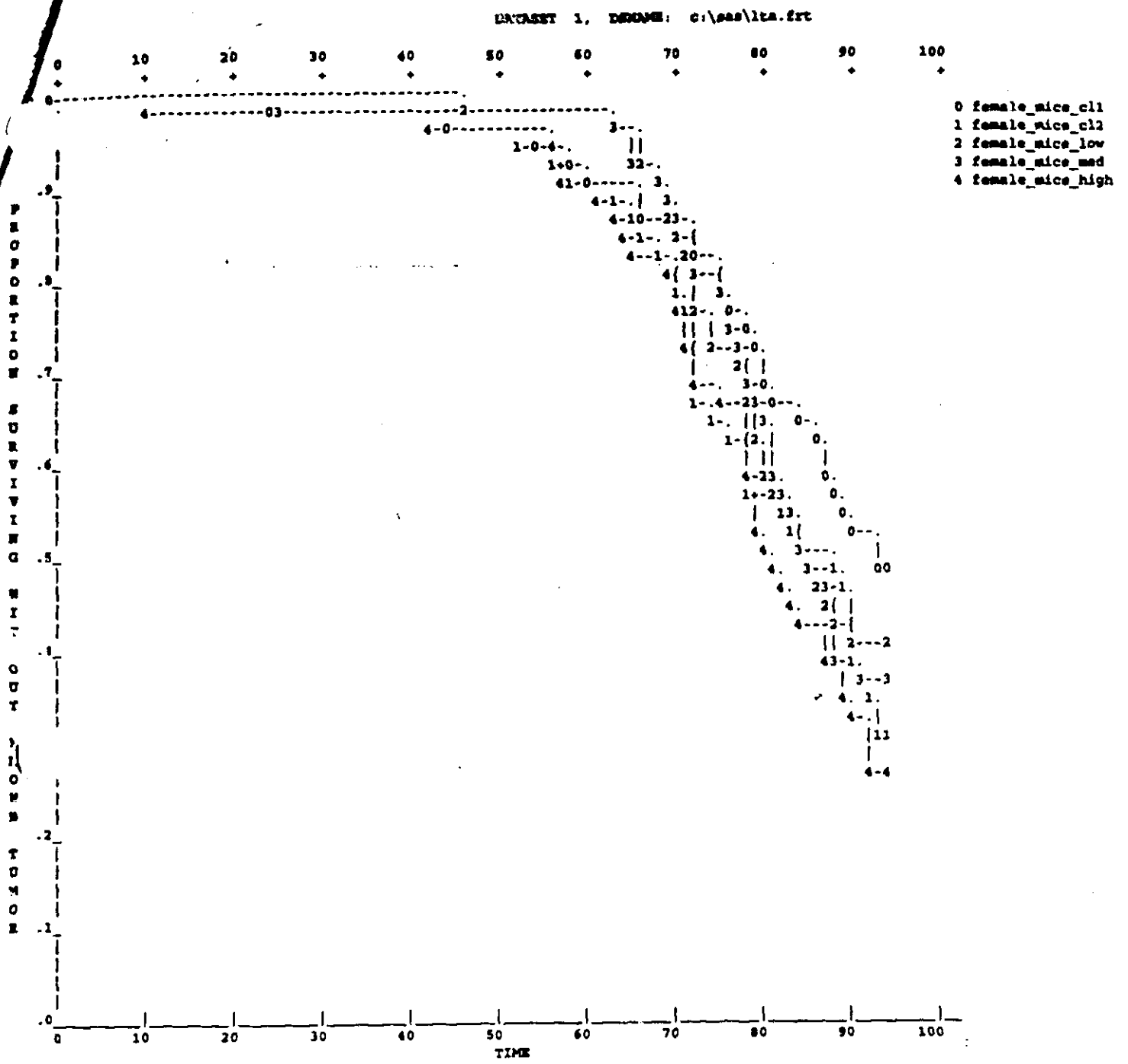

Figure 4: Female Mice Survival Curves

Table 6
Results of Tumor Data Analysis
(Excluding Interim Sacrifice Data)
The Mouse Study

Sex/Tissue/Tumor Type (Total Tumor Counts)	p-Value of Exact Permutation Trend Test "incidental"	"fatal"	"combined"
MALES			
Leiomyosarcoma of Urinary Bladder	.014 (1,0,0,4)	--	--
FEMALES			
Leiomyosarcoma of Urinary Bladder	.006 (1,0,3,0,6)	NS (0,0,0,1,0)	.008 (1,0,3,1,6)

Executive Carcinogenicity Assessment Committee Meeting
August 8, 1995

Committee members: Joseph DeGeorge, Acting Chair (HFD-150)
Joseph F. Contrera (HFD-400)
Anwar Goheer (HFD-007)
Sharon Olmstead, Exec Sec (HFD-001)

The following information reflects a brief summary of the committee discussion and its recommendations. For detailed study information, reference should be made to the individual reviews submitted to the committee.

NDA 20-505 (Fisher; Fitzgerald)
Topamax (topiramate)
R.W. Johnson

The sponsor provided carcinogenicity data from a 104-week rat study and a 93 and 94 week study the female and male mouse, respectively. The duration of the mouse study was shorten to 93 weeks for females and 94 weeks for males, following a 70% mortality in the HD mice. A steph infection has been identified as the cause of the high number of deaths.

The doses for the rat study were 20, 45, and 120 mg/kg. The findings were negative for mutagenicity and clastogenicity. There were not reported increases in tumor incidence in the rat.

The doses for the mouse were 20, 75, and 300 mg/kg. No clinical signs were reported and only a small change in body weight was seen. The mice did experience liver toxicity, nephrotoxicity and an induction effect. The tumor findings were significant for urinary bladder. The tumors may be smooth muscle in origin and species specific. This type of tumor is not aggressive in animals. The division has recommended including the urinary bladder findings from the HD males and LD and HD females in the labeling.

The committee agreed that the study designs and the dose selections were adequate. Dr. DeGeorge requested that the division call NTP or NCTR and inquire about their standard practice of reporting leiomyosarcomas and combining the tumor across organs.

Dr. Fitzgerald spoke with Gary Boorman at NIEHS regarding the leiomyosarcomas. He indicated that leiomyosarcomas should not be combined across all organs. Although one might do a second analysis if they occurred within an organ system, such as kidney and bladder, esophagus and intestinal tract, uterus and vagina, etc.

9/11/95

Joseph DeGeorge, Ph.D.
Acting Chair, CAC

CARCINOGENICITY

A) TWO YEAR CARCINOGENICITY STUDY IN MICE (A500736; GLP; Vols. 29-33)

1. Treatment

Mice were dosed with 0 (C I), 0 (C II), 20, 75, or 300 mg/kg, in the diet, for 53 weeks (10/sex/group) or 93-95 weeks (60/sex/group). The HD was based on the MTD in a 6-month pilot study; the LD is the estimated daily therapeutic dose. Study duration was shortened to ensure adequate numbers for evaluation.

Strain: Crl: CD-1(ICR)BR, VAF/Plus
Drug Lot #: 8806672

2. Mortality

Study mortality rates were approximately 50-70%. No treatment effect was observed in males. Survival was decreased in HD females compared to C I, but not compared to C II or combined controls. (See FDA statistical review).

Mortality Incidence

Dose (mg/kg)	Male (Week 94)	Female (Week 93)
0 (control I)	36	31
0 (control II)	35	42
20	36	36
75	29	38
300	32	44

3. Observed Signs

No treatment-related clinical signs. Staph infection found in all groups.

4. Body Weight

BW means intermittently lower (5-10%) in treatment groups compared to controls throughout the study; however, no differences in terminal BWs.

5. Food Consumption

No drug-related changes in food consumption.

6. Tissue Mass Observations

No drug-related changes in palpable masses.

7. Clinical Pathology

Only serum gastrin measured, at interim and terminal sacrifices. Mean gastrin levels increased (40%) in HD females at study termination.

8. Gross Pathology

a) 1-Year Interim Sacrifice

No gross findings related to treatment.

b) Terminal Sacrifice

i. Stomach - Thickened mucosa was found in 1/60 MD and 3/60 HD males. A nodule was observed in 1 HD male.
ii. Kidney - Incidences of renal discoloration, enlargement, capsular irregularities, and pelvic dilatation or hydronephrosis were increased in treated females. Uroliths were seen in one MD and one HD female.
iii. Urinary bladder - Distension was observed only in treated females, in 4/60, 5/60, and 9/60 of LD, MD, and HD, respectively.
iv. Spleen - The incidence of splenic enlargement was increased in treated males.

9. Microscopic Pathology

Complete microscopic examinations performed on all groups except C I; examination of C I limited to urinary bladder.

a) 1-Year Interim Sacrifice

i. Liver - Hepatocellular hypertrophy was seen in 1/59, 2/60, 5/60, and 8/60 males in the C II, LD, MD, and HD groups, respectively.
ii. Stomach - The incidence of dilated gastric fundic glands was increased in treated males and females. Lymphocytic infiltration and amyloidosis of the gastric mucosa were increased in treated females. A hyperplastic diverticulum was found in fundic submucosa of one HD male.
iii. Kidney - Renal tubular dilatation was increased in HD females.
iv. Urinary bladder - No proliferative changes were found at 1 year.

b) Terminal Sacrifice

Non-neoplastic

i. Liver - The incidence of hepatocellular hypertrophy was increased in HD males (27/60) and MD (5/60) and HD females (18/60) compared to controls (9/59 males, 0/60 females). The incidence of hepatocellular hyperplasia was increased in HD males (6/60 vs 1/59 in C). Hepatic extramedullary hematopoiesis was increased in treated females.
ii. Stomach (body) - The incidence of gastric mucosal (generative-cell zone) hyperplasia was increased in MD and HD males (33/60 & 45/60) and females (20/60 & 38/60) compared to C (1/59 & 2/60 in M & F). The incidence of focal hyperplastic diverticula was increased in HD males (9/60 vs 3/59 in C).
iii. Kidney - Incidences of renal pelvic dilatation and chronic pyelonephritis or chronic glomerulonephritis were increased in HD females.
iv. Urinary bladder - Increased incidences of chronic or hyperplastic cystitis (5/59 HD♀s vs 0/120 C), focal mucosal hyperplasia (6/60 HD♂s vs 0/117

C; 4/60 MD, 6/59 HD♀s vs 1/120 C), calculi (2/59 HD♀s vs 0/120 C), and dilatation of the lumen (2/57, 3/60, & 5/59 in LD, MD, & HD♀s, respectively, vs 0/120 C) were observed in treated mice.

v. Spleen - The incidence of splenic hyperplasia was slightly increased at the HD.

Neoplastic

i. Urinary bladder - Tumor incidence was increased in HD males (0/59 & 1/59 controls vs 4/60 HD) and in females from all treatment groups (1/60 & 1/60 in controls vs 3/60, 2/60, & 9/60 in LD, MD, HD), largely due to the occurrence of lesions originally diagnosed as leiomyosarcomas (Table 1). Statistical significance was reached for leiomyosarcomas in HD males and LD and HD females, and for all bladder tumors in HD females (see statistical review).

ii. Other - Low incidences of the following tumors were observed in drug-treated groups only: squamous cell carcinoma of (fore)stomach in males (1, 1, & 2 in LD, MD, & HD), splenic hemangiosarcoma (1 LD male, 1 MD & 1 HD female), malignant meningioma (1 HD male), hepatocellular carcinoma in females (1 HD), and renal tubular carcinoma (1 HD male).

Table 1: Incidence of Primary Neoplasms in the Mouse Urinary Bladder

Dose (mg/kg/day)	0	0	20	75	300	0	0	20	75	300
Sex:	M	M	M	M	M	F	F	F	F	F
No./Group:	59	59	60	60	60	60	60	60	60	60
Tumor Type:										
carcinoma (transitional cell)	0	0	0	0	0	0	0	0	0	1
hemangiosarcoma	0	0	0	0	0	0	0	0	0	1
leiomyoma	0	0	0	0	0	0	1	0	0	0
leiomyosarcoma	0	1	0	0	4	1	0	3	1	6
papilloma	0	0	0	0	0	0	0	0	0	1
polyp, stromal	0	0	0	0	0	0	0	0	1	0
Total Incidence	0	1	0	0	4	1	1	3	2	9

10. Drug exposure

In a separate toxicokinetics study, CD-1 mice (27/sex/group) received topiramate doses of 20, 75, or 300 mg/kg/day, in the diet, for 1 month. Terminal blood samples were collected from 3/sex/group every 3 hr for 24 hr, and plasma drug levels were measured.

Dose (mg/kg/day)	Plasma AUC (ug·hr/ml; mean ± SEM)	
	Male	Female
20	11.2 ± 0.7	2.5 ± 0.4
75	55.1 ± 4.7	12.6 ± 1.8
300	225.3 ± 15.7	133.2 ± 14.7

Data indicated nearly continuous exposure at all doses, although levels showed considerable circadian variation. Male plasma AUC values were greater (1.7-4.5-fold) than those for females at each dose level. Approximately proportional increases in female AUCs were seen between the LD and MD, but the increase was much greater than proportional between the MD and HD. In males, exposure increased less than dose-proportionally between the LD and HD, but proportionally between the MD and HD.

B) TWO YEAR CARCINOGENICITY STUDY IN RATS (A500737; GLP; Vols. 26-28)

1. Treatment

50 rats/sex were dosed with 0 (C I), 0 (C II), 20, 45, or 120 mg/kg, in the diet, for 104-105 weeks. The HD was based on toxicity in the 12-month oral toxicity study; LD is the estimated daily clinical dose.

Strain: Wistar [Crl:(WI)BR, VAF/Plus]
Drug Lot #: 8806672

2. Mortality

Survival was not decreased by drug administration (see statistical review).

Mortality Incidence

Dose (mg/kg)	Male	Female
0 (contol I)	20	24
0 (control II)	28	22
20	19	18
45	15	17
120	15	22

3. Observed Signs

No drug-related clinical signs noted.

4. Body Weight

Decreased in MD and HD females (final means 6 & 21%, respectively, below C II) and in HD males (7% below C II). Smaller decreases seen in LD females, primarily between weeks 23 and 81, and in LD & MD males, primarily during the first year.

5. Food Consumption

No drug-related effects in males. Decreased in HD females throughout most of study.

6. Ophthalmoscopic Exam

No treatment-related effects.

7. Tissue Mass Observations

No drug-related changes in number of palpable masses.

8. Clinical Pathology

Only gastrin levels were measured. Mean serum gastrin levels were increased compared to control (C I) levels in HD (70%) males at 57 weeks and in MD (40%) and HD (100%) males and HD females (50%) at week 105.

9. Gross Pathology

Pleural foci in the lungs were increased in HD males. Increased numbers of HD males and females had mucoid stomach contents. A prominent limiting ridge was noted in the stomachs of several HD males. The incidence of renal pelvic calculi was increased in males and females from all treatment groups. Sediment in the urinary bladder lumen and dilatation of the bladder were increased in HD males.

10. Microscopic Pathology

Complete microscopic examinations performed on all groups except C I.

a) Non-neoplastic

i. Liver - Increased incidences of centrilobular hepatocellular hypertrophy (0, 3, 16, 16/50 in C, LD, MD, HD males, respectively; 0, 0, 17, 33/50 in corresponding females), vacuolization (9/50 MD, 7/50 HD vs 2/50 C females), and eosinophilic foci (23/50 HD vs 10/50 C males; 5, 15, 16, 15/50 in C, LD, MD, HD females, respectively) were found in treated rats.

ii. Stomach - Increased incidences of hyperplasia of the generative cell zone of the fundic gastric glands (5, 6, 24, 45/50 in C, LD, MD, HD male, respectively; 4, 8, 39, 47/50 in corresponding females), decreased parietal cells, inflammatory cell infiltration, and hyperplasia of the limiting ridge between the forestomach and fundus were found in MD and HD groups.

iii. Kidney - The incidence of renal calculi was increased in HD males (23/50 vs 10/50 in C) and in treated females (38, 43, 50, 47/50 of C, LD, MD, HD, respectively). D-R increase in severity in both sexes. Incidence of urothelial hyperplasia was increased in HD males (23/50 vs 13/50 C) and

in females at all doses (24, 31, 35. 29/50 in C, LD, MD, HD, respectively).

iv. Urinary bladder - Incidences of calculi (2/50 HD M, 1/50 HD F), mucosal hyperplasia (0/50, 1/49, 2/49, 3/50 in C, LD, MD, HD males, respectively; 2, 1, 1, 4/50 in respective females) and dilation of the urinary bladder (4, 3, 7, 8 in C, LD, MD, HD males, respectively) were higher in treated rats.

b) Neoplastic

There was no statistically significant increase in the incidence of any tumor type (see statistical review).

i. Urinary bladder - Mucosal papilloma was observed in one male in each of the MD and HD groups and in one HD female, possibly secondary to chronic irritation induced by calculi in the lumen. A leiomyosarcoma was found in 1 MD female.

ii. Other - Single incidences of renal tubular carcinoma (1 HD female) and squamous cell carcinoma of (fore)stomach (1 HD female) were found only in treatment groups.

SUMMARY

Mouse

CD-1 mice were administered topiramate doses of 0 (C I), 0 (C II), 20, 75, or 300 mg/kg, in the diet, for 53 (10/sex/group) or 93-95 weeks (60/sex/group). Study duration was shortened due to high mortality (50-70%). There were no group differences in survival for males, but mortality was increased in HD females compared to one of the two control groups. BWs were slightly (<10%) decreased in HD groups compared to controls throughout the study. No treatment-related clinical signs were noted.

At the 1-year interim sacrifice, hepatocellular hypertrophy was increased dose-dependently in treated males. Dilated gastric fundic glands, lymphocytic infiltration, amyloidosis of the stomach mucosa, and hyperplastic diverticulum were present more often in treated mice. In addition, renal tubular dilatation was increased in HD females.

At study termination, gastrin levels were found to be slightly elevated in HD females, and treatment-related non-neoplastic morphologic changes were seen in the liver, stomach, kidneys, and urinary bladder, primarily of MD and HD group mice. These included: (1) hepatocellular hypertrophy (MD, HD) and hyperplasia (HD males); (2) hyperplasia of the mucosal generative cell zone (MD, HD), lymphocytic infiltration (MD, HD), and focal hyperplastic diverticula (HD males) in the body of the stomach; (3) gross kidney changes, renal pelvic dilatation, and chronic pyelonephritis or glomerulonephritis (all in HD females); and (4) urinary bladder calculi (2 HD females), chronic or hyperplastic cystitis (HD females), focal mucosal bladder hyperplasia (HD males; MD & HD females), and dilatation of the lumen of the urinary bladder (females at all doses).

The incidence of urinary bladder tumors was increased in HD males (4/60 vs 0/59 & 1/59 in controls) and in females from all treatment groups (3/60, 2/60, & 9/60 in LD, MD, HD, respectively, vs 1/60 & 1/60 in controls). Statistical significance was reached for leiomyosarcomas in HD males and LD and HD females, and for all bladder tumors in HD females. There was no evidence of metastasis. The predominant tumor type, first diagnosed as a leiomyosarcoma, was examined by consultant pathologists and determined to be histomorphologically unique to mice. Single incidences of other types of bladder tumors (transitional cell carcinoma, papilloma, hemangiosarcoma) were found only in HD females (see **Table 1**).

At the HD used in this study, 24-hr plasma AUCs measured in satellite groups were 225 and 133 ug·hr/ml in males and females, respectively. AUCs as high as 475 ug·hr/ml have been measured in clinical trials in patients receiving 400 mg/kg bid of topiramate.

Rat

Wistar rats (50/se/group) were administered topiramate doses of 0 (C I), 0 (C II), 20, 45, or 120 mg/kg, in the diet, for 104-105 weeks. Survival was not affected by drug treatment and was adequate for study validity (>50%). BWs were decreased in HD males (terminal mean 7% below C II) and in MD and HD females (final means 6 & 21% below C II). Serum gastrin levels were increased in HD males at 1 year and in MD and HD males and HD females at the end of treatment. No drug-related clinical signs were noted.

At study termination, treatment-related non-neoplastic morphologic changes were seen in the liver, stomach, kidneys, and urinary bladder. These included: (1) hepatocytic hypertrophy (males at all doses, MD & HD females) and vacuolization (MD & HD females), and liver eosinophilic-cell foci (HD males, females at all doses); (2) hyperplasia of the generative cell zone of gastric glands in the body of the stomach, with an associated decrease in parietal cells and inflammatory cell infiltration, and hyperplasia of the limiting ridge between the forestomach and fundus (all at MD & HD); (3) renal calculi and hyperplasia of the pelvic and papillary urothelium (HD males; females at all doses); and (4) calculi (HD), mucosal hyperplasia (HD), and dilatation of the urinary bladder (MD & HD males).

There were no statistically significant increases in tumor incidence, but mucosal papillomas were found in the urinary bladders of 1 MD and 1 HD male and 1 HD female, possibly secondary to chronic irritation induced by calculi in the bladder lumen. In addition, a urinary bladder leiomyosarcoma was found in 1 MD female, a renal tubular carcinoma in 1 HD female, and a squamous cell carcinoma of the forestomach in 1 HD female.

Blood levels were not determined for this study, but in satellite toxicokinetic groups for the 12-month rat toxicology study, administration (diet) of topiramate to Wistar rats at doses of 10, 55, and 300 mg/kg for 3 months produced 24-hr serum AUCs of 28, 145, and 356 ug·hr/ml, respectively, in males, with corresponding values of 79, 361, 1083 ug·hr/ml in females.

EVALUATION

The incidence of urinary bladder tumors was increased in topiramate-treatment mice in the 21-month study (statistical significance was reached for HD males and LD and HD females). This was largely due to the increased occurrence of a tumor that was initially diagnosed as a leiomyosarcoma but that was considered unusual from a histomorphologic standpoint. These lesions were described as variable-sized nodular proliferations of large pleomorphic cells in the submucosa and muscular wall of the bladder. None of the nodules had metastasized, and only one was visible grossly. Although its incidence was increased in treated mice, this bladder lesion was also seen in two controls. When they were examined by outside experts (hired by the sponsor), there was no agreement on whether or not the lesions in question were really leiomyosarcomas or even neoplastic, but all three consultants indicated that they were unique to mice and of little or no clinical significance. One pathologist determined that only two of the lesions were malignancies, one control and one HD. Spontaneous and induced urinary bladder tumors in experimental animals and humans are predominantly transitional cell carcinomas; smooth muscle tumors are uncommon, and the type seen in the topiramate study has apparently only been described in mice, particularly in Swiss-derived strains such as the one used in this study. Chandra and Frith (1991) reported a very low spontaneous incidence of bladder tumors with the same morphological characteristics as those in the present study, in CD-1 mice. Because the bladder lesions in the topiramate study were always accompanied by inflammatory changes and often by urothelial hyperplasia, one consultant concluded that they represented a proliferative response to chronic irritation. Calculi were found in the bladders of two HD

females with tumors. An association between the presence of calculi (or various other physical and chemical irritants) in the bladder lumen and the development of bladder epithelial hyperplasia and neoplasia is well established in rodents. For example, urothelial hyperplasia and bladder tumors seen in mice treated with 4-ethylsulfonylnaphthalene-1-sulfonamide (ENS) have been linked to urine alkalinization and calculus formation resulting from inhibition of CA by ENS. Neutralizing the urine with ammonium chloride reportedly prevented urolithiasis and the development of hyperplasia and tumors in ENS-treated mice. Urothelial hyperplasia has been seen after administration of other CA inhibitors such as acetazolamide to rodents (but not rabbits, dogs, or monkeys) and may in some cases progress to neoplasia. These bladder effects were also thought to be secondary to the changes in urine composition produced by CA inhibition. Since topiramate is a CA inhibitor and has been shown to elevate urine pH and induce calculus formation and urothelial hyperplasia in rodents, a similar pathogenesis of bladder neoplasia in topiramate-treated mice seems likely. Although most of the bladder tumors increased by topiramate treatment were of a type regarded as species specific, single incidences of hemangiosarcoma, transitional cell papilloma, and transitional cell carcinoma in HD female mice indicate that the bladder proliferative changes produced by topiramate may sometimes (but rarely) progress to tumors with human relevance. No statistically significant increase in tumors was seen in the rat carcinogenicity study, but transitional cell papillomas found in the urinary bladders of 1 MD and 2 HD rats and single incidences of urinary bladder leiomyosarcoma (MD) and renal tubular carcinoma (HD) could have been related to the alterations in urinary physiology produced by topiramate, as described above. Glandular mucosal hyperplasia of the stomach was seen in both the mouse and the rat carcinogenicity studies, but there was no evidence of progression to neoplasia. The stomach tumors seen in these studies primarily involved the forestomach. Genotoxicity results for topiramate in a full battery of tests were negative except for a slight increase in chromosomal aberrations in the *in vivo* rat cytogenicity assay, supporting an epigenetic mechanism for the induction of bladder tumors by topiramate. In view of the low incidence of bladder tumors with human relevance associated with topiramate administration to mice, and their probable etiology, the findings do not indicate that the drug presents a significant carcinogenic risk to patients.

RECOMMENDATIONS

A description of the mouse bladder tumor finding should be included in the topiramate labeling. The following is suggested:

Carcinogenesis, Mutagenesis, Impairment of Fertility

> When topiramate was given to mice in the diet at doses of 20, 75, or 300 mg/kg/day for 21 months, a statistically significant increase in the incidence of urinary bladder tumors was observed in males receiving the highest dose and in females from the low and high dose groups. This was largely due to the increased occurrence of a bladder tumor type considered histomorphologically unique to mice; therefore, the relevance of this finding to human carcinogenic risk is uncertain. The doses used in the mouse study are approximately 0.1-1.5 times the maximum human daily dose (MHDD) on a mg/m2 basis. The high dose was associated with plasma topiramate exposures of 225 and 133 ug·hr/ml in male and female mice, respectively. Exposures as high as 475 ug·hr/ml have been measured in patients receiving MHDD of topiramate. No evidence of carcinogenicity was seen in rats following oral administration of topiramate for 2 years at doses up to 120 mg/kg/day or approximately 1.2 times the MHDD on a mg/m2 basis. Topiramate did not demonstrate mutagenic or genotoxic potential in a battery of *in vitro* and *in vivo* assays. No adverse effects on fertility were observed in rats at doses up to 100 mg/kg, or approximately 1 times the MHDD on a mg/m2 basis.

cc:
NDA (20-505)
Div File
HFD-120/GFitzgerald/EFisher/RPitts

J.E. Fisher, Ph.D.

TWENTY-FOUR MONTH ONCOGENICITY STUDY OF TOPIRAMATE

ADMINISTERED AS A DIETARY ADMIXTURE TO MICE

STUDY NO: 1337

TUMOR SUMMARY - FEMALE

ORGAN - TUMOR DIAGNOSIS	NUMBER OF ANIMALS				
	GRP1	GRP2	GRP3	GRP4	GRP5
ADRENAL GLAND-CORTEX ADENOMA	0	0	1	0	0
*BONE (OTHER) FIBROSARCOMA	0	0	0	0	1
*BRAIN GLIOMA	0	1	0	0	0
*CERVIX CARCINOMA	0	0	0	1	0
CERVIX LEIOMYOMA	0	0	0	3	2
*CERVIX LEIOMYOSARCOMA	0	0	1	0	0
CERVIX POLYP	0	2	0	0	1
*LACRIMAL/HARDERIAN GL ADENOCARCINOMA	0	1	0	0	0
LACRIMAL/HARDERIAN GL ADENOMA	0	2	0	0	1
LIVER HEMANGIOMA	0	2	1	1	1
*LIVER HEMANGIOSARCOMA	0	1	1	1	0
*LIVER HEPATOCELLULAR CARCINOMA	0	0	0	0	1
LUNG BRONCHIOLO-ALVEOLAR ADENOMA	0	5	5	3	4
*LUNG BRONCHIOLO-ALVEOLAR CARCINOMA	0	0	2	1	2
LYMPH NODE MESENTERIC HEMANGIOMA	0	0	0	1	0
*LYMPHORETICULAR SYSTEM HISTIOCYTIC SARCOMA	1	1	0	0	0
*LYMPHORETICULAR SYSTEM SYSTEMIC LYMPHOSARCOMA	2	9	8	4	7
*LYMPHORETICULAR SYSTEM THYMIC LYMPHOSARCOMA	0	3	0	1	3
*MAMMARY GLAND ADENOACANTHOMA	0	0	1	0	0
*MAMMARY GLAND ADENOCARCINOMA	0	2	0	1	0
*MEDIASTINUM OSTEOGENIC SARCOMA	0	0	0	0	1
OVARIES ADENOMA	0	0	0	1	0
OVARIES HEMANGIOMA	0	0	0	0	1
OVARIES OVIDUCT LEIOMYOMA	0	0	1	0	0
OVARIES LUTEOMA	0	0	0	0	1
OVARIES PAPILLARY ADENOMA	0	1	0	0	0
OVARIES THECOMA	0	0	0	1	0
PITUITARY GLAND PARS DISTALIS ADENOMA	0	0	1	0	0
SKIN/SUBCUTIS (GROSS LESION) FIBROMA	0	0	1	0	0
*SKIN/SUBCUTIS (GROSS LESION) SCHWANNOMA	0	0	0	0	1
SPLEEN HEMANGIOMA	0	0	0	0	1
*SPLEEN HEMANGIOSARCOMA	0	0	0	1	1
*STOMACH (FORESTOMACH) SQUAMOUS-CELL CARCINOMA	0	1	0	0	0
STOMACH (PYLORUS) ADENOMATOUS POLYP	0	1	0	0	0
THYROID GLAND FOLLICULAR ADENOMA	0	1	0	0	0
*URINARY BLADDER HEMANGIOSARCOMA	0	0	0	0	1
URINARY BLADDER LEIOMYOMA	0	1	0	0	0
*URINARY BLADDER LEIOMYOSARCOMA	1	0	3	1	6
URINARY BLADDER PAPILLOMA	0	0	0	0	1
URINARY BLADDER STROMAL POLYP	0	0	0	1	0
*URINARY BLADDER TRANSITIONAL-CELL CARCINOMA	0	0	0	0	1
*UTERUS ENDOMETRIAL ADENOCARCINOMA	0	1	1	1	0
UTERUS ENDOMETRIAL POLYP	0	3	6	5	2
UTERUS HEMANGIOMA	0	1	0	2	3
UTERUS LEIOMYOMA	0	1	2	2	1
*UTERUS LEIOMYOSARCOMA	0	0	0	0	2
*UTERUS SCHWANNOMA	0	0	0	0	1
*VAGINA CARCINOMA	0	0	1	0	0
*VAGINA LEIOMYOSARCOMA	0	1	0	0	0
*VAGINA SCHWANNOMA	0	0	0	1	0
VULVA PAPILLOMA	0	0	0	1	0

DOSE: GROUP1 - 0 MG/KG
GROUP2 - 0 MG/KG
GROUP3 - 20 MG/KG
GROUP4 - 75 MG/KG
GROUP5 - 300 MG/KG

NOTE: * DENOTES A MALIGNANT TUMOR
BENIGN OTHERWISE

ADMINISTERED AS A DIETARY ADMIXTURE TO MICE

STUDY NO: 1337

TUMOR SUMMARY - MALE

ORGAN - TUMOR DIAGNOSIS	NUMBER OF ANIMALS				
	GRP1	GRP2	GRP3	GRP4	GRP5
ADRENAL GLAND-CORTEX ADENOMA	0	1	1	0	0
*BONE (OTHER) HEMANGIOSARCOMA	0	0	1	0	0
BONE (OTHER) ODONTOMA	0	0	0	1	0
BRAIN MENINGIOMA	0	0	0	1	0
*BRAIN MENINGIOMA	0	0	0	0	1
EPIDIDYMIDES SCHWANNOMA	0	0	1	0	0
*HEART HEMANGIOSARCOMA	0	0	1	0	0
*KIDNEYS TUBULAR CARCINOMA	0	0	0	0	1
LACRIMAL/HARDERIAN GL ADENOMA	0	1	2	9	2
*LIVER HEMANGIOSARCOMA	0	3	2	1	0
LIVER HEPATOCELLULAR ADENOMA	0	7	8	6	8
*LIVER HEPATOCELLULAR CARCINOMA	0	3	2	1	1
LUNG BRONCHIOLO-ALVEOLAR ADENOMA	0	8	10	5	13
*LUNG BRONCHIOLO-ALVEOLAR CARCINOMA	0	1	2	2	1
LYMPH NODE MESENTERIC HEMANGIOMA	0	0	1	0	0
*LYMPHORETICULAR SYSTEM HISTIOCYTIC SARCOMA	0	0	1	0	0
*LYMPHORETICULAR SYSTEM SYSTEMIC LYMPHOSARCOMA	0	1	1	4	1
PANCREAS ISLET-CELL ADENOMA	0	2	0	0	0
PROSTATE ADENOMA	0	0	1	0	0
SKIN/SUBCUTIS (GROSS LESION) BASAL-CELL TUMOR	0	0	1	0	0
SKIN/SUBCUTIS (GROSS LESION) CYSTADENOMA	0	0	0	1	0
SKIN/SUBCUTIS (GROSS LESION) HEMANGIOMA	0	0	0	0	1
*SKIN/SUBCUTIS (GROSS LESION) HEMANGIOSARCOMA	0	0	0	2	0
*SKIN/SUBCUTIS (GROSS LESION) UNDIFFERENTIATED SARCOMA	0	0	0	0	1
SPLEEN HEMANGIOMA	0	0	1	0	0
*SPLEEN HEMANGIOSARCOMA	0	0	1	0	0
*STOMACH (FORESTOMACH) SQUAMOUS-CELL CARCINOMA	0	0	1	1	2
TESTES ADENOMA	0	1	0	0	0
TESTES INTERSTITIAL-CELL TUMOR	0	0	0	1	0
THYROID GLAND C-CELL ADENOMA	0	1	0	0	0
THYROID GLAND FOLLICULAR ADENOMA	0	0	0	1	1
*URINARY BLADDER LEIOMYOSARCOMA	0	1	0	0	4

DOSE: GROUP1 - 0 MG/KG
GROUP2 - 0 MG/KG
GROUP3 - 20 MG/KG
GROUP4 - 75 MG/KG
GROUP5 - 300 MG/KG

NOTE: * DENOTES A MALIGNANT TUMOR
BENIGN OTHERWISE

TWENTY-FOUR MONTH ONCOGENICITY STUDY OF TOPIRAMATE

ADMINISTERED AS A DIETARY ADMIXTURE TO RATS

STUDY NO: 1356

TUMOR SUMMARY - FEMALE

ORGAN - TUMOR DIAGNOSIS	NUMBER OF ANIMALS			
	GROUP1	GROUP2	GROUP3	GROUP4
ABDOMINAL CAVITY HEMANGIOMA	0	0	0	1
ABDOMINAL CAVITY LIPOMA	0	0	0	1
ADRENAL GLAND-CORTEX ADENOMA	2	0	0	2
ADRENAL GLAND-MEDULLA MEDULLARY TUMOR(S)	1	0	1	1
CECUM MUCOSAL POLYP	1	0	0	0
CERVIX GRANULAR-CELL TUMOR	0	1	0	0
CERVIX LEIOMYOMA	1	0	0	0
CERVIX POLYP	0	2	0	0
*CERVIX SCHWANNOMA	0	0	1	0
DUODENUM LEIOMYOMA	0	0	1	0
*JEJUNUM LEIOMYOSARCOMA	0	0	0	1
KIDNEYS MESENCHYMAL, MIXED TUMOR	2	0	0	0
*KIDNEYS TUBULAR CARCINOMA	0	0	0	1
LIVER CHOLANGIOMA	0	0	1	0
LIVER HEPATOCELLULAR ADENOMA	1	1	2	1
*LYMPHORETICULAR SYSTEM HISTIOCYTIC SARCOMA	1	1	0	0
*LYMPHORETICULAR SYSTEM MALIGNANT FIBROUS HISTIOCYTOMA	1	0	0	0
*LYMPHORETICULAR SYSTEM SYSTEMIC LYMPHOSARCOMA	0	0	0	1
*LYMPHORETICULAR SYSTEM THYMIC LYMPHOSARCOMA	6	3	0	1
*MAMMARY GLAND ADENOCARCINOMA	9	3	4	1
MAMMARY GLAND ADENOMA	4	2	0	1
MAMMARY GLAND CYSTADENOMA	1	0	0	0
MAMMARY GLAND FIBROADENOMA	16	8	8	6
*MUSCLE HEMANGIOSARCOMA	0	0	1	0
OVARIES GRANULOSA-THECA-CELL TUMOR	0	2	0	2
OVARIES INTERSTITIAL-CELL TUMOR(S)	1	0	0	0
OVARIES OVIDUCT ADENOMA	0	0	1	0
OVARIES SCHWANNOMA	0	1	0	0
OVARIES SERTOLI-CELL TUMOR	1	1	0	1
OVARIES THECOMA	1	0	0	0

TWENTY-FOUR MONTH ONCOGENICITY STUDY OF TOPIRAMATE

ADMINISTERED AS A DIETARY ADMIXTURE TO RATS

STUDY NO: 1356

TUMOR SUMMARY - FEMALE

ORGAN - TUMOR DIAGNOSIS	NUMBER OF ANIMALS			
	GROUP1	GROUP2	GROUP3	GROUP4
PANCREAS ISLET-CELL ADENOMA	1	2	1	0
*PANCREAS ISLET-CELL CARCINOMA	1	0	0	0
PARATHYROID GLAND ADENOMA	1	0	0	0
*PITUITARY GLAND PARS DISTALIS ADENOCARCINOMA	2	0	1	0
PITUITARY GLAND PARS DISTALIS ADENOMA	28	27	21	22
PITUITARY GLAND PARS INTERMEDIA ADENOMA	1	0	0	0
SKIN/SUBCUTIS (GROSS LESION) BASAL-CELL TUMOR	2	0	0	0
SKIN/SUBCUTIS (GROSS LESION) FIBROMA	0	0	1	0
*SKIN/SUBCUTIS (GROSS LESION) HEMANGIOSARCOMA	0	1	0	0
SKIN/SUBCUTIS (GROSS LESION) KERATOACANTHOMA	0	1	0	0
SKIN/SUBCUTIS (GROSS LESION) LIPOMA	0	1	0	0
SKIN/SUBCUTIS (GROSS LESION) PAPILLOMA	1	0	2	0
*SKIN/SUBCUTIS (GROSS LESION) SCHWANNOMA	0	0	1	0
SKIN/SUBCUTIS (GROSS LESION) SEBACEOUS GLAND ADENOMA	0	1	0	0
*STOMACH (FORESTOMACH) SQUAMOUS-CELL CARCINOMA	0	0	0	1
*THORACIC CAVITY CARCINOSARCOMA	0	0	1	0
THYMUS EPITHELIAL THYMOMA	0	1	0	0
THYROID GLAND C-CELL ADENOMA	4	5	7	6
*THYROID GLAND C-CELL CARCINOMA	1	0	0	0
*THYROID GLAND FOLLICULAR ADENOCARCINOMA	0	0	1	1
THYROID GLAND FOLLICULAR-CELL ADENOMA	0	1	1	0
*URINARY BLADDER LEIOMYOSARCOMA	0	0	1	0
URINARY BLADDER PAPILLOMA	0	0	0	1
*UTERUS ENDOMETRIAL ADENOCARCINOMA	0	0	1	0
UTERUS ENDOMETRIAL POLYP	10	4	8	10
UTERUS FIBROMA	1	0	0	0
UTERUS SCHWANNOMA	1	0	0	0
*UTERUS SCHWANNOMA	0	3	1	2
VAGINA GRANULAR-CELL TUMOR	0	0	0	1
VAGINA HEMANGIOMA	0	0	0	1
VAGINA POLYP	0	2	0	0
*VAGINA SCHWANNOMA	0	0	1	0

DOSE: GROUP1 - 0 MG/KG
GROUP2 - 20 MG/KG
GROUP3 - 45 MG/KG
GROUP4 - 120 MG/KG

NOTE: * DENOTES A MALIGNANT TUMOR
BENIGN OTHERWISE

TWENTY-FOUR MONTH ONCOGENICITY STUDY OF TOPIRAMATE

ADMINISTERED AS A DIETARY ADMIXTURE TO RATS

STUDY NO: 1356

TUMOR SUMMARY - MALE

ORGAN - TUMOR DIAGNOSIS	NUMBER OF ANIMALS			
	GROUP1	GROUP2	GROUP3	GROUP4
ABDOMINAL CAVITY FIBROMA	0	1	0	0
ADRENAL GLAND-CORTEX ADENOMA	1	0	0	0
ADRENAL GLAND-MEDULLA MEDULLARY TUMOR(S)	4	5	1	6
*ADRENAL GLAND-MEDULLA MEDULLARY TUMOR(S)	2	1	1	0
BONE (OTHER) OSTEOMA	1	0	0	1
BRAIN GRANULAR-CELL TUMOR	1	1	0	0
*BRAIN MALIGNANT RETICULOSIS	1	0	1	1
*BRAIN MENINGIOMA	0	0	1	0
*EYES FIBROSARCOMA	0	1	0	0
*HEART SCHWANNOMA	1	0	0	0
*JEJUNUM MUCINOUS ADENOCARCINOMA	0	2	0	1
KIDNEYS MESENCHYMAL, MIXED TUMOR	1	1	0	0
*KIDNEYS MESENCHYMAL, MIXED TUMOR	0	1	0	0
KIDNEYS TUBULAR ADENOMA	0	1	0	1
LIVER HEPATOCELLULAR ADENOMA	1	0	1	1
*LUNG SQUAMOUS-CELL CARCINOMA	0	0	1	0
*LYMPH NODE MESENTERIC HEMANGIOSARCOMA	0	1	0	0
*LYMPHORETICULAR SYSTEM HISTIOCYTIC SARCOMA	0	0	0	1
*LYMPHORETICULAR SYSTEM MALIGNANT FIBROUS HISTIOCYTOMA	0	1	0	0
*LYMPHORETICULAR SYSTEM SYSTEMIC LYMPHOSARCOMA	1	0	0	1
*LYMPHORETICULAR SYSTEM THYMIC LYMPHOSARCOMA	1	1	1	1
*MAMMARY GLAND ADENOCARCINOMA	1	1	0	0
MAMMARY GLAND FIBROADENOMA	0	0	1	0
*MESENTERY HEMANGIOSARCOMA	0	0	1	0
MUSCLE HEMANGIOMA	0	0	0	1
PANCREAS ACINAR ADENOMA	3	3	4	0
PANCREAS ISLET-CELL ADENOMA	2	6	4	1
*PANCREAS ISLET-CELL CARCINOMA	0	0	1	0
*PITUITARY GLAND MENINGIOMA	0	0	1	0
PITUITARY GLAND PARS DISTALIS ADENOMA	20	17	21	10
PITUITARY GLAND PARS INTERMEDIA ADENOMA	0	0	1	0
PREPUTIAL GLAND ADENOMA	1	0	0	0
PROSTATE ADENOMA	0	0	2	1
*SKIN/SUBCUTIS (GROSS LESION) BASAL-CELL CARCINOMA	0	1	0	0
SKIN/SUBCUTIS (GROSS LESION) BASAL-CELL TUMOR	2	0	0	0
SKIN/SUBCUTIS (GROSS LESION) FIBROMA	2	1	1	2
*SKIN/SUBCUTIS (GROSS LESION) FIBROSARCOMA	2	1	2	0
SKIN/SUBCUTIS (GROSS LESION) HEMANGIOMA	0	0	0	1
*SKIN/SUBCUTIS (GROSS LESION) HEMANGIOSARCOMA	1	3	1	0
SKIN/SUBCUTIS (GROSS LESION) HISTIOCYTOMA	1	0	0	0
SKIN/SUBCUTIS (GROSS LESION) KERATOACANTHOMA	2	2	7	0
SKIN/SUBCUTIS (GROSS LESION) LIPOMA	1	0	0	1
*SKIN/SUBCUTIS (GROSS LESION) LYMPHANGIOSARCOMA	0	1	1	0
*SKIN/SUBCUTIS (GROSS LESION) NOS SARCOMA	0	0	1	0
SKIN/SUBCUTIS (GROSS LESION) PAPILLOMA	3	0	0	0
SKIN/SUBCUTIS (GROSS LESION) SCHWANNOMA	0	0	1	2
*SKIN/SUBCUTIS (GROSS LESION) SQUAMOUS-CELL CARCINOMA	1	0	0	1
*SPLEEN HEMANGIOSARCOMA	0	1	0	0
*STOMACH (BODY) LEIOMYOSARCOMA	0	1	0	0
TESTES INTERSTITIAL-CELL TUMOR(S)	5	7	5	7
THYMUS EPITHELIAL THYMOMA	0	1	0	0
THYROID GLAND C-CELL ADENOMA	4	9	5	5
*THYROID GLAND C-CELL CARCINOMA	0	2	1	0
*THYROID GLAND FOLLICULAR ADENOCARCINOMA	0	1	0	0
THYROID GLAND FOLLICULAR-CELL ADENOMA	0	1	2	0
TONGUE LIPOMA	0	1	0	0
URINARY BLADDER PAPILLOMA	0	0	1	1

DOSE: GROUP1 - 0 MG/KG
GROUP2 - 20 MG/KG
GROUP3 - 45 MG/KG
GROUP4 - 120 MG/KG

NOTE: * DENOTES A MALIGNANT TUMOR
BENIGN OTHERWISE