APPENDIX 1

Mutagenicity Consult

MULTICASE QSAR Analysis

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service
FDA's Center for Drug Evaluation and Research (CDER),
Office of Testing and Research (OTR), Regulatory Research and Analysis Staff (RRAS)

Consult Structure Activity Review

Date: April 10, 1998

From: Edwin J. Matthews, Ph.D., Toxicologist (HFD-901) &
Joseph F. Contrera, Ph.D., Associate Director (HFD-901)

Requesting Reviewer & Division: Thomas D. Steele, Ph.D.
HFD-120

NDA: NDA 20,864

Sponsor: Merck

Compound Name(s): Rizatriptan and Rizatriptan-N-oxide

SAR Software System: FDA/CDER Enhanced *MULTI-CASE* Software Program developed under Cooperative Research and Development Agreement (CRADA) between OTR and Multicase, Inc.

Background Information

This review is an assessment of the potential activity of rizatriptan and rizatriptan-N-oxide metabolite in the *MULTI-CASE* Quantitative Structure Activity Relationship (QSAR) software program Rodent Carcinogenicity Test. This test estimates the potential carcinogenicity of an organic compound in a standard four cell rodent carcinogenicity test which includes male and female rats and mice. The test was conducted by FDA/CDER's Office of Testing and Research (OTR), Regulatory Research and Analysis Staff (RRAS). The *MULTI-CASE* QSAR program used in this study has been modified and enhanced by OTR under a CRADA between OTR and Multicase, Inc., and it is now an automated human expert/QSAR system.

MULTI-CASE QSAR Carcinogenicity Test

The *MULTI-CASE* program performs four different tests on query compounds. First, it determines whether query organic compounds are covered, *ie.* whether all query molecule 2-10 atom fragments are represented in molecules in the control data module. If a query compound has two or more unknown fragments not included in the control database molecules, *MULTI-CASE* is unable to provide a reliable estimate of the query compound's potential carcinogenicity. Second, the program identifies any 2-10 atom fragments in the query molecule that are structure alerts (SA) for carcinogenicity. These SA are pre-determined by the program by comparing all 2-10 atom fragments in non-carcinogenic and carcinogenic molecules in the control database module. If the query compound has SA, they are classified in terms of trans-gender and trans-specie activities in rodents. Third, the program compares the local molecular environment of query compound SA and issues warnings if these SA have molecular

environments from that are significantly different from SA in the control database carcinogens. Finally, the program identifies any molecular fragments that are highly correlated with the suppression of carcinogenicity (*i.e.*, deactivating fragments).

OTR's classification of activities of carcinogens in control database modules and the *MULTI-CASE* QSAR test results are both based upon a weight of evidence method modeled after the Tennant hypothesis (Tennant, R.W. Mutation Research 286:111-118, 1993). In this hypothesis the relative carcinogen potency and likelihood of being a human carcinogen is proportional to a compound's trans-gender, trans-species, and multiple tumor site response in rodents. The OTR classification method designates compounds with single cell/single site tumor responses as marginal tumor responses. Furthermore, the OTR method assigns scaled CASE units of carcinogenic activity to carcinogens in proportion to trans-gender, trans-species, and multiple tumor site responses.

Results

Test System: The QSAR Carcinogenicity Test was conducted using Version 3.11 of both the *MULTI-CASE* program and the four OTR rodent carcinogenicity database modules, including: AF5 (male rat), AF6 (female rat), AF7 (male mouse), and AF8 (female mouse). The results of the *MULTI-CASE* program prediction experiment saved in an ASCII summary file ("J-file") and a comprehensive data file ("R-file").

Predictivity/Performance: OTR recently performed a beta-test on the *MULTI-CASE* program and 4-OTR carcinogenicity modules using 53 compounds with carcinogenicity studies that were not included in the control modules. The studies included 42 drugs and 11 NTP compounds, and the coverage for this dataset was 93%. The positive predictivity for carcinogenic compounds was 86%, and it detected 6/7 compounds correctly. The negative predictivity of the program for non-carcinogenic compounds was 97%, and it detected 35/36 compounds correctly. In total, the program correctly predicted 41/53 compounds, and it had an overall concordance of 77%.

Assay Evaluation Criteria: The results of the four OTR module experiments are evaluated individually as: inactive "-", possibly active/indeterminate "(+)", and "+" active. These activities are based upon both the statistical significance (frequency of appearance) and the biologic potency (average CASE unit activity) of SA detected in a query compound. The classification of individual SA for carcinogenicity were pre-determined and dependent upon the activities of control carcinogens in male and female rats and mice. OTR's rank-order of the biologic potency of SA specifies: gender specific (**gs**) SA $<<$ trans-gender (**tg**) SA $<<$ trans-specie (**ts**) SA. After the results from the four individual experiments have been evaluated, these results are consolidated to obtain an overall prediction of activity in the *MULTI-CASE* QSAR test. OTR's recommended criteria for a positive response in this test requires a query compound be evaluated as "+" active in $\geq$ two rodent carcinogenicity modules. In contrast, a query compound is evaluated as "-" for all lesser responses in the four modules.

OTR Reviewer's Appraisal: The results of the *MULTI-CASE* Rodent Carcinogenicity Test on a query compound are divided into three parts, including an assessment of *a)* coverage, *b)* the presence of any gender/specie rodent carcinogenicity SA, and *c)* an overall estimate of potential carcinogenicity in rodents. In this study rizatriptan was observed to be completely

covered and all of its 2-10 atom fragments were represented in all 4 OTR database modules (see **Table 1**). In contrast, the N-oxide metabolite of rizatriptan was not covered, and each of the 4-OTR database modules detected the same 3 unknown fragments (*ie.*, OH-N^+-; OH-N^+-CH2-; and OH-N^+-CH3). The only N-oxide in our CDER carcinogenicity database is 4-nitroquinoline-N-oxide, a potent trans-specie rodent carcinogen, but the structure of this compound is considerably different from the rizatriptan-N-oxide in this study (see **Figure 1**). Because the N-oxide fragments were not represented in the control database modules, *MULTI-CASE* could not predict the potential carcinogenicity of this compound.

Summary: The results of this study showed that rizatriptan did not have any structure alerts correlated with rodent carcinogenicity. Therefore, rizatriptan is not predicted to be a trans-gender and/or trans-species rodent carcinogen, and it is evaluated as inactive in the *MULTI-CASE* QSAR Rodent Carcinogenicity Test. In contrast, *MULTI-CASE* could not predict the potential carcinogenicity of rizatriptan-N-oxide metabolite of rizatriptan because this compound had three unknown molecular fragments.

[redacted]

cc C Bové (OTR Files)

EJ Matthews: 4/8/98: C:\WPFILES\TEST\20864.1: DRAFT (4/9/98): Comments (Contrera): FINAL 4/10/98

Table 1. Summary of results of evaluating Rizatriptan and N-oxide Metabolites in the *MULTI-CASE* QSAR Carcinogenicity Test

OTR Module[1]	Rizatriptan Structure Alerts[2] W	#	CASE Act.	Frequency [T,I,M,A]	Atoms	OTR Call[3] gs/tg/ts	Act.
Rizatriptan							
AF5 (♂R)	0	NONE					-
AF6 (♀R)	0	NONE					-
AF7 (♂M)	0	NONE					-
AF8 (♀M)	0	NONE					-
Rizatriptan N-oxide Metabolite							
AF5 (♂R)	3	NONE					NA
AF6 (♀R)	3	NONE					NA
AF7 (♂M)	3	NONE					NA
AF8 (♀M)	3	NONE					NA

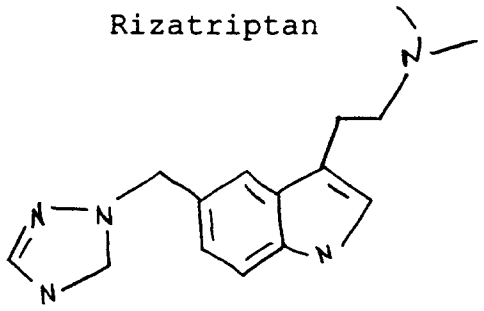
[1] **OTR Module**: The four OTR rodent carcinogenicity database modules are described under **Test System** above.

[2] **Structure Alert**: The *MULTI-CASE* program identifies five attributes of query compound, rodent carcinogenicity SA, including: *a)* the number of unknown ("W") 2-10 atom fragments; *b)* the SA number, *c)* the average biologic potency in CASE units, *d)* the frequency of appearance in carcinogens in control database modules, and *e)* the 2-10 atom composition. The SA number is a sequential number assigned by the *MULTI-CASE* program when it identifying SA in carcinogen molecules in each rodent carcinogenicity database module. The CASE unit activities are based on a log-response that assigns active compounds , inactive compounds 10-19 units, and marginally active compounds . The frequency of the SA in the control database is represented in terms of the total ("**T**"), inactive ("**I**"), marginal ("**M**"), and active ("**A**") molecules which contained the SA. Aliphatic atoms in SA are presented in capital letters; aromatic atoms are presented in lower case letters.

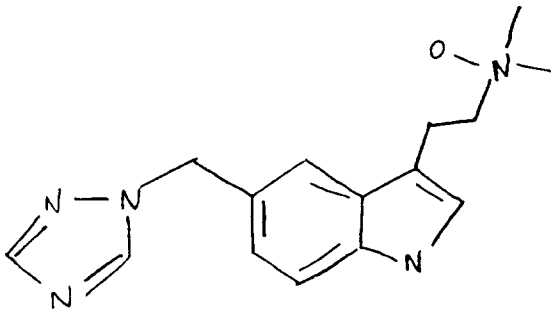
[3] **OTR Call**: The method used to evaluated the results of the individual OTR module experiments is explained under **Assay Evaluation Criteria** above.

Figure 1 Comparison of the structures of Rizatriptan and two N-oxide compounds

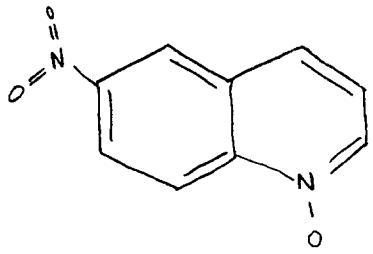
Rizatriptan



Rizatriptan-N-oxide



4-Nitroquinoline oxide



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DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
Original Summary

NDA No.: 20865 **Submission Date:** 6/30/97
Review Date: 5/7/98

Drug: MAXALT™ (rizatriptan benzoate) RAPIDISC (5 and 10 mg)

Sponsor: Merck & Co.
P.O. Box 4, BLA-20
West Point, PA 19486

Reviewer: T.D. Steele

Indication: acute treatment of migraine attacks with and without aura

Pharmacologic Class: 5-$HT_{1B/D}$ agonist

Related INDs, NDAs: IND NDA 20864

Chemical Information:

CAS Number: 145202308-66-0

IUPAC Name: N,N-Dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine monobenzoate

Other Names: MK-0462; L-705,126-004B

Empirical Formula: $C_{15}H_{19}N_5O_5 \cdot C_7H_6O_2$

Molecular Weight: 391.47

Nonclinical Pharmacology and Toxicology Studies Reviewed:

Cross-reference to Pharm/Tox review of NDA 20864. No additional studies related to the RAPIDISC formulation were required. The excipients in the RAPIDISC formulation are GRAS substances and a common flavoring agent, none of which would require additional testing.

RECOMMENDATION

The NDA is approvable.

/S/

Thomas D. Steele, Ph.D.
Pharmacologist/Toxicologist

Original NDA 20864S
cc.: /Division File, HFD-120
/G. Fitzgerald, Ph.D.
/L.Chen, R.Ph.
/T.D. Steele, Ph.D.
/S/ 5/8/98

APPENDIX 2

Agency Statistical Review

Chen

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Statistical Review and Evaluation

Carcinogenicity Review of Rizatriptan Benzoate
Rat and Mouse Studies for Both Male and Female

APR 8 1998

DATE:

NDA #: 20-864, Animal Carcinogenicity Studies.

DRUG NAME: Rizatriptan Benzoate (MAXALT®).

SPONSOR: Merck Research Laboratories.

INDICATION FOR THE HUMAN USE: Alleviation of Migraine Headache

TREATMENT GROUPS: For both male and female rats and mice the treatments are: a control and MAXALT doses at 2, 25, and 125 mg/kg/day.

DOCUMENTS REVIEWED: Carcinogenicity Study Reports, Vol. 1.25, 1.26, 1.27.

This review has been discussed with Dr. Thomas Steele, Pharmacologist from the Division of Neuropharmacological Drug Products (**HFD-120**).

For the statistical analyses, this reviewer used the Carcinogenicity Evauation Program, Version of March 10, 1998, developed by Dr. Ted Guo, Mathematical Statistician from the Division of Biometrics II (**HFD-715**).

Organization

The following describes this review's organization:

Section 1: **Introduction**

Section 2: **Rat Study**

- **2.1.** Design, Clinical and Statistical Procedures
  - **2.1.1.** Design
  - **2.1.2.** Clinical Procedure
  - **2.1.3.** Statistical Procedure
- **2.2.** Sponsor's Analysis and Conclusion for Males and Females
  - **2.2.1.** Mortality/Survival Analysis
  - **2.2.2.** Tumor Trend Analysis
- **2.3.** Reviewer's Analysis and Conclusion
  - **2.3.1.** Male Rats
  - **2.3.1.1.** Mortality/Survival Analysis
  - **2.3.1.2.** Tumor Trend Analysis
- **2.3.2.** Female Rats
  - **2.3.2.1.** Mortality/Survival Analysis
  - **2.3.2.2.** Tumor Trend Analysis
- **2.3.3.** Validity of Study Design

Section 3: **Mouse Study**

- **3.1.** Study Design
  - **3.1.1.** Design
  - **3.1.2.** Clinical Procedure
  - **3.1.3.** Statistical Procedure
- **3.2.** Sponsor's Analysis and Conclusion for Males and Females
  - **3.2.1.** Mortality/Survival Analysis
  - **3.2.2.** Tumor Trend Analysis
- **3.3.** Reviewer's Analysis and Conclusion
  - **3.3.1.** Male Mice
    - **3.1.1.1.** Mortality/Survival Analysis
    - **3.3.1.2.** Tumor Trend Analysis
  - **3.3.2.** Female Mice
    - **3.3.2.1.** Mortality/Survival Analysis
    - **3.3.2.2.** Tumor Trend Analysis
  - **3.3.3.** Validity of Study Design

Section 4: **Reviewer's Conclusion**

1. INTRODUCTION

Rizatriptan Benzoate, with the trade name of **MAXALT** is indicated for the alleviation of migraine headaches in human use. The animal studies in this NDA consist of a 106-week oral carcinogenicity study in male and female Sprague-Dawley rats (Study TT #94-060-0[E-1]) and a100-week oral carcinogenicity study in male and female CD-1 mice (Study TT #94-061-0-1 [E-2]).

2. RAT STUDY

2.1. Design, Clinical and Statistical Procedures

2.1.1. Design and its Validity

This is a 106-week study in Sprague-Dawley male and female rats with the objective of assessing the oncogenic/carcinogenic potential of MAXALT. There were four treatment groups consisting of a control and MAXALT doses at 2, 25, and 125 mg/kg/day, with 100 animals in the control group and 50 in each treatment group.

2.1.2. Clinical Procedure

During the study, the rats were observed daily for mortality and weekly for clinical signs. Rats were examined for the presence of palpable masses every four weeks, beginning in Drug Week 26. A complete necropsy was performed on all animals.

The terminal sacrifice for the male and female rats was started and ended at week 105.

2.1.3. Statistical Procedure

The statistical test for survival was conducted at $\alpha = 0.05$. The statistical test for the incidences of the various types of tumors was performed at $\alpha = 0.05$, with adjustment for multiple testing (see Footnote 3).

2.2. Sponsor's Results and Conclusion

The sponsor's analyses include mortality and tumors trend analysis. The results are summarized below:

2.2.1. Mortality/Survival Analysis

The following table presents the sponsor's summary of the percent mortality during the study.

Table I (2.2.1): Percent (%) of Mortality/Survival During the Study

		Males				Females			
		Cont.	2 mg	25 mg	125 mg	Cont.	2 mg	25 mg	125 mg
Mortality/ Survival (%)	Found Dead Up to Week 104	33	19	18	24	33	21	20	26
	Survived at Week 104	67	31	32	26	67	29	30	24
	Total	100	50	50	50	100	50	50	50
	Trend Test P-Value ¤	--	--	0.422	**0.049**	--	--	0.173	**0.028**

¤: The P-values resulted from the pairwise log-rank test comparing the doses with the control.

The sponsor's survival analysis consists of sequential pairwise log-rank tests at $\alpha = 0.05$, to compare mortality in MAXALT doses with the control. The method proceeds from the high to low dose. From the results, the sponsor concluded that there is a significant difference in mortality in the MAXALT 125 mg/kg/day groupas compared to the control ($P < 0.05$).

Comment: As will be seen in the reviewer's analysis, this reviewer performed an overall log-rank test which included all treatments in the analysis. The reviewer's analysis did not find a significant difference among doses.

2.2.2. Tumor Trend Analysis

The tumor trend test was performed, separately, for "arithmetic", "Logarithmic" and "Ordinal" scales. The reported P-value was the smallest P-value amongst the three P-values generated by the three analyses (one analysis for each dose scaling). The tests were one-sided at α=0.05; however, extra P-value adjustments were considered for the multiplicity testing. The method has been discussed by Heyse[1] and Harter[2]. **In conclusion, the sponsor found no significant tumor trend.**

Comment: In his analyses, this reviewer also did not find any statistically significant dose related tumor trend. However, in reaching the conclusion, he used the criteria discussed in the FDA's Guideline, which is different from the sponsor's[3].

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[1]- Heyse, J.F. and Rom, D. "Adjusting for multiplicity of statistical tests in the analysis of carcinogenicity studies.", *Biometrical Journal,* Vol. 30, 1988; 883-896.

[2]- Harter H. L. "Error rates and sample sizes for range tests in multiple comparisons.", *Biometrics,* Vol. 13, 1957; 13, 511-536.

[3]- By the FDA's Guidance for Industry on the Statistical Aspects of Design, Analysis, and Interpretation of Animal Carcinogenicity Studies:

i. Tumors with the spontaneous incidence rate of > 1% (based on historical observations or based on observations in the control groups) are considered as **common**. Then, the choice of significance level will be $\alpha' = 0.01$ for the pairwise comparisons and $\alpha' = 0.005$ for the trend analysis.

Statistical Reviewer: Kooros Mahjoob

2.3. Reviewer's Analysis and Conclusion

Similar analyses were performed for the male and female rats (similarly for the male and female mice). However, a separate discussion will be presented for the males and females.

The analyses consist of:

1. Mortality/survival analyses which consist: (i) Kaplan-Meier estimate of the survival Function; (ii) Dose-Mortality Trend Test, using both Cox Regression and Non-Parametric Kruskal-Wallis methods. The analysis was conducted with all treatments included as well as for the pairwise comparison of the high dose with the control.

2. Organ-tumor trend analysis, according to the Peto's method[4], adjusted for possible differences in survival between the groups by partitioning the 106 weeks into the sub-intervals 0-52, 53-78, 79-91, 92-104, 105-106. The analysis presents the Exact as well as the Asymptotic P-values for the dose related organ-tumor trend. The detailed results of the analyses are presented in **Appendix A (Male-Rats)** and **Appendix B (Female-Rats)**.

Comments: (i) There are substantial differences between the **Exact** and **Asymptotic** P-values for the cases that there were very small incidences of the tumor, such as one or two animals with the tumor in the high dose. For such cases, the use of asymptotic results is inappropriate and hence, this reviewer uses the exact P-values to reach his conclusion. (ii) Overall, there was no statistically significant dose related organ-tumor trend; however, there were cases that **P > 0.05** for exact, but **P < 0.05** for the asymptotic. Although the exact p-values should be used for the conclusion, for the purpose of not omitting any noticeable finding, those cases were extracted from Appendix A (Male-Rats) and Appendix B (Female-Rats) and are displayed in a table in the main body of this review.

2.3.1. Male Rats

2.3.1.1. Mortality/Survival Analysis

Table II (2.3.1.1) displays the distribution of the number and the percent of the male rats which either died during the Weeks 1 to 104 or were terminally sacrificed during Week 105.

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ii. Tumors with the spontaneous incidence rate of ≤ 1% (based on historical observations or based on observations in the control groups) are considered as **rare**. Then, the level of significance should be set at $\alpha' = 0.05$ for the pairwise comparisons and at $\alpha' = 0.025$ for the trend analysis.

[4]- Peto, R. et al. "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments". In Long-Term and Short-Term Screening Assays for Carinogens: A Critical Appraisal, International Agency for Research on Cancer, Lyon, France. IARC Monographs Supplement 2, 1980; 311- 426.

TABLE II (2.3.1.1.) Distribution of Number and % of Male Rats Died or Terminally Sacrificed.

Week	Control			2 mg/kg/day			25 mg/kg/day			125 mg/kg/day			No. Died Total
	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	
0-52	100	7	7.0	50	1	2.0	50	4	8.0	50	2	4.0	14
53-78	93	6	6.0	49	4	8.0	46	3	6.0	48	8	16.0	21
79-91	87	15	15.0	45	4	8.0	43	1	2.0	40	5	10.0	25
92-104	72	5	5.0	41	10	20.0	42	10	20.0	35	9	18.0	34
Terminal■ Sacrifice	67	67	67.0	31	31	62.0	32	32	64.0	26	26	52.0	156

■: The number of animals terminally sacrificed is the same as the number of animals survived after week 104.

From the columns of % of animal died, it appears that there is no dose related mortality. This can also be seen from **Figure I (2.3.1.1.)** and more objectively, from Figure II (2.3.1.1.), the Kaplan-Meier estimates of the survival function.

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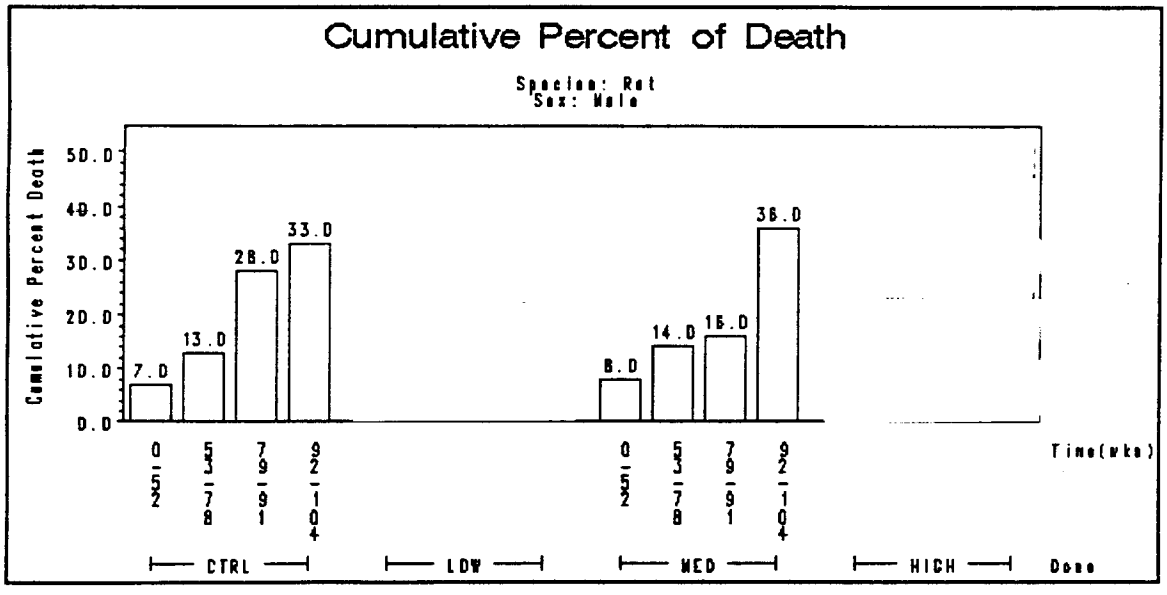
FIGURE I (2.3.1.1.) Cumulative Distribution of Percent of Male Rats Died During the Study



Statistical Reviewer: Kooros Mahjoob

FIGURE II (2.3.1.1.) Kaplan-Meier Estimate of the Survival Function for the Male Rats

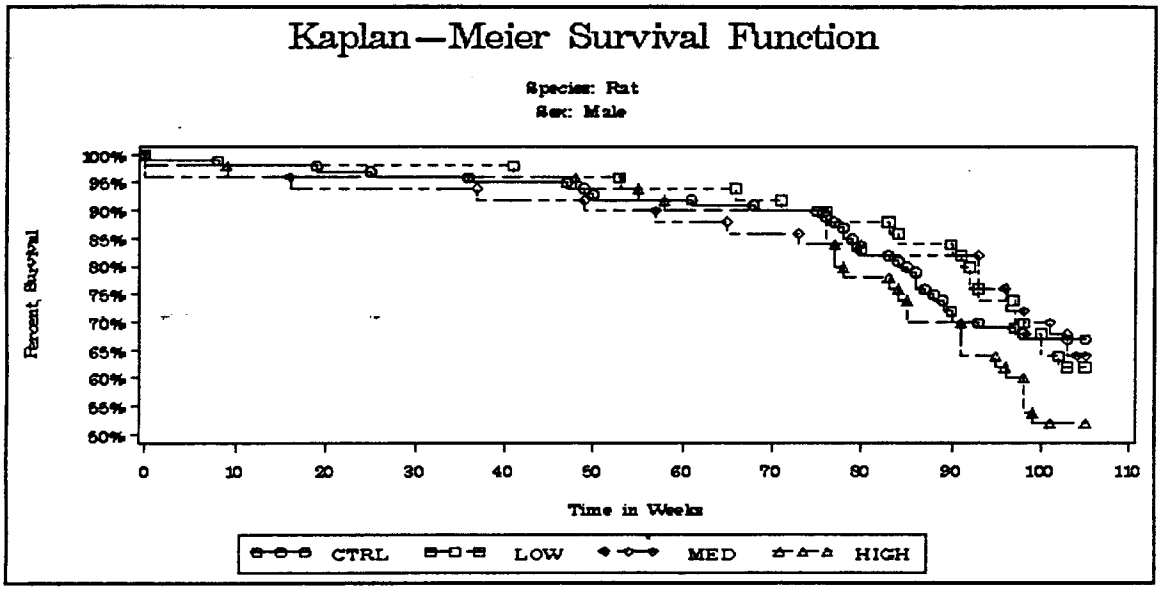


Figure II (2.3.1.1.) shows the homogeneity of the survival distributions in the 4 treatment groups.

The results of Cox Regression and Non-Parametric Kruskal-Wallis are summarized in **Table III (2.3.1.1.)**. The results indicate that there is no evidence of a statistically significant dose related mortality trend (P>0.05).

Comment: For the comparison of the high dose with the control, the sponsor's analysis found a significant trend with P = 0.049. But, in the reviewer's analysis for the same comparison, P ≥ 0.1589 for both Cox Regression and Kruskal-Wallis tests.

TABLE III (2.3.1.1.) Dose Related Mortality Trend Test for Male Rats

Method	Time Adjusted Trend-Test	All Treatments Included		High Dose vs. Control	
		Statistics	P-Value	Statistics	P-Value
Cox	Dose-Mortality Trend	2.73	0.0983	1.98	0.1589
	Departure From Trend	0.17	0.9201	--	--
	Homogeneity	2.90	0.4073	--	--
Kruskal-Wallis	Dose-Mortality Trend	2.34	0.1259	1.77	0.1838
	Departure From Trend	0.13	0.9277	--	--
	Homogeneity	2.47	0.4805	--	--

2.3.1.2. Tumor Trend Analysis

Overall, the results have not shown any statistically significant dose related trend for the observed organ-tumor cases. By reading through **Table I.A (Male-Rats)** of Appendix A (Male-Rats), there were four cases that the analysis resulted in P <0.05 for either the "exact", "asymptotic" or both P-values. Those are summarized in **Table IV (2.3.1.2.).**

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TABLE IV (2.3.1.2.): Somewhat Noticeable Tumor Trends in Male Rats

ORGAN TYPE	TUMOR TYPE	Number of Incidences Per Treatment				Incidental or Fatal	Rare or Common ¤	Trend Analysis P-Values		125 mg vs Control Exact P-Value
		Cont	2 mg	25 mg	125 mg			Exact	Asymp-totic	
Pancreas Islet	Adenoma	10	8	5	10	IN	C	0.0493	0.0448	0.0432
Skin Sebaceous Gland	Adenoma	0	0	0	1	IN	R	0.1667	0.0145	0.2796
Pleura	Mesothelioma	0	0	0	1	FA	R	0.1775	0.0177	0.3061
Stomach Nonglandular Muco	Papilloma	0	0	0	1	IN	R	0.2000	0.0233	0.2500

¤ : Considered as a common tumor if the incidental rate is > 1% historically or in Control Group.

Using the FDA's criteria (see Footnote 3): Pancreas' Islet tumor is a common tumor and is not significant. The rest are also not significant, by using the Exact P-values.

A pairwise comparison between the high dose and the control was performed and the results are presented in the last column of Table IV (2.3.1.2.). The resulting P-values further support the assertion of no statistically significant tumor trend. Thus, the overall conclusion is:

The results provide no evidence of a statistically significant dose related tumor trend.

2.3.2. Female Rat

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2.3.2.1. Mortality/Survival Analysis

Table V (2.3.2.1), on the next page, displays the distribution of the number and the percent of the female rats which either died during the weeks 1 to 104 or were terminally sacrificed during Week 105.

Similar to the case for the male rats, as Table V (2.3.2.1) shows, from the comparison among doses, with respect to the % of animals died, it appears that there is no dose related mortality trend. This also can be seen from **Figure III (2.3.2.1.)** which displays the cumulative distribution of the percent of rat death and from **Figure IV (2.3.2.1.),** the Kaplan-Meier estimates of the survival function.

TABLE V (2.3.2.1.) Distribution of Number of Female Rats Died or Terminally Sacrificed

Week	Control			2 mg/kg/day			25 mg/kg/day			125 mg/kg/day			No. Died Total
	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	
0-52	100	3	3.0	50	3	6.0	50	2	4.0	50	1	2.0	9
53-78	97	7	7.0	47	5	10.0	48	2	4.0	49	6	12.0	20
79-91	90	8	8.0	42	4	8.0	46	8	16.0	43	5	10.0	25
92-104	82	15	15.0	38	9	18.0	38	7	14.0	38	13	26.0	44
Terminal■ Sacrifice	67	67	67.0	29	29	58.0	31	31	62.0	25	25	50.0	152

■: The number of animals terminally sacrificed is the same as the number of animals survived after week 104.

FIGURE III (2.3.2.1.) Cumulative Distribution of Percent of Female Rats Died During the Study

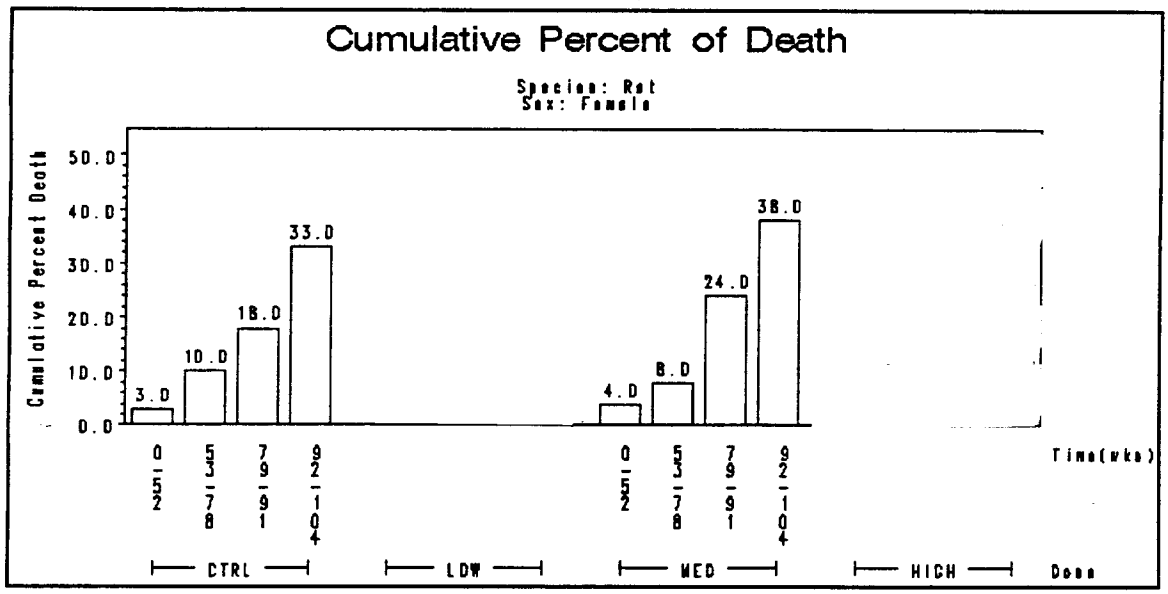

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FIGURE IV (2.3.2.1.) Kaplan-Meier Estimate of the Survival Function for the Female Rats

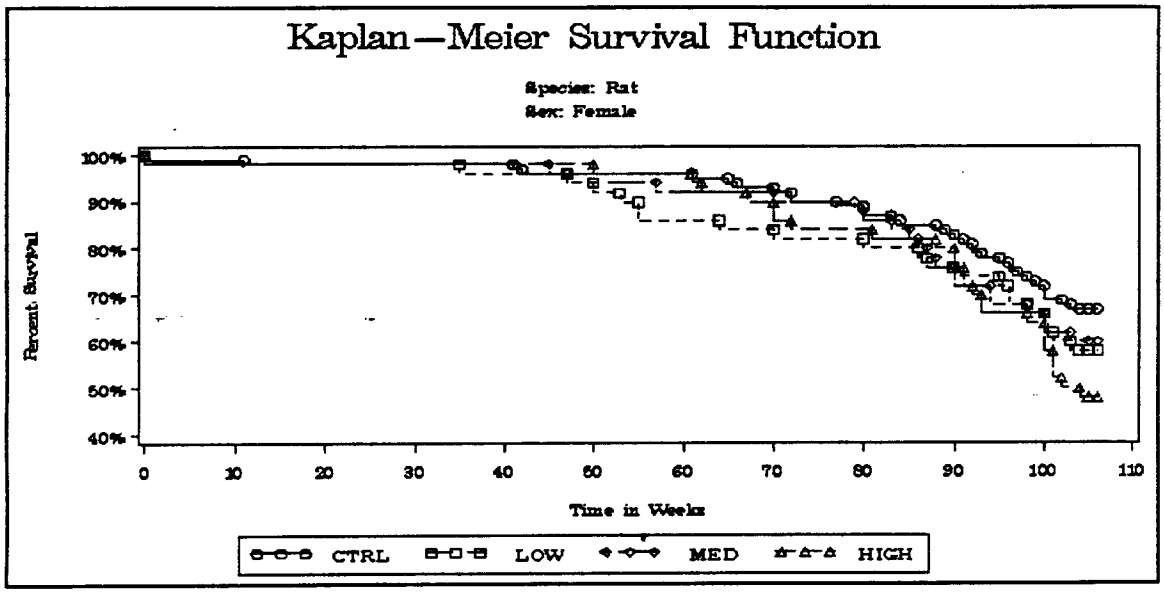

Figure IV (2.3.2.1.) shows the homogeneity of the survival distributions in the 4 treatment groups.

The results of Cox Regression and Non-Parametric Kruskal-Wallis are summarized in **Table VI (2.3.2.1.)**. The results indicate that there is no evidence of a statistically significant dose related mortality trend (P>0.05).

Comment: For the comparison of the high dose with the control, the sponsor's analysis found a significant trend with P = 0.028. But, in the reviewer's analysis for the same comparison, P ≥ 0.0787 for both Cox Regression and Kruskal-Wallis tests.

TABLE VI (2.3.2.1.) Dose Related Mortality Trend Test for the Female Rats

Method	Time Adjusted Trend-Test				
		Statistics	P-Value	Statistics	P-Value
Cox	Dose-Mortality Trend	2.58	0.1081	3.09	0.0787
	Departure From Trend	1.12	0.5711	--	--
	Homogeneity	3.70	0.2955	--	--
Kruskal-Wallis	Dose-Mortality Trend	1.96	0.1613	3.08	0.0795
	Departure From Trend	1.23	0.5411	--	--
	Homogeneity	3.19	0.3632	--	--

2.3.2.2. Tumor Trend Analysis

Overall, the results have not shown any statistically significant dose related trend for the observed organ-tumor cases. By reading through **Table I.B (Female-Rats)** of Appendix B (Female-Rats), there were four cases such that analysis resulted in P <0.025 for either the "exact", "asymptotic" or both P-values. Those are summarized in **Table VII (2.3.2.2.).**

TABLE VII (2.3.2.2.): Somewhat Noticeable Tumor Trends in Female Rats

ORGAN TYPE	TUMOR TYPE	Number of Incidences Per Treatment				Incidental or Fatal	Rare or Common ¤	Trend Analysis P-Values		125 mg vs Control Exact P-Value
		Cont	2 mg	25 mg	125 mg			Exact	Asymp-totic	
Uterus	Sarcoma	0	1	0	1	FA	R	0.0484	0.0220	0.0909
Brain	Granular Cell Tumor	0	0	0	1	IN	R	0.1645	0.0139	0.2717
Skin	Fibroma	0	0	0	1	IN	R	0.1645	0.0139	0.2717
Skin	Osteogenic Sarcoma	0	0	0	1	FA	R	0.1822	0.0209	0.3077

¤ : Considered as a common tumor if the incidental rate is > 1% historically or in Control Group.

Now using the FDA's criteria (see Footnote 3) and the Exact P-values, one may conclude that the trends for these organ-tumor cases are not significant.

A pairwise comparison between the high dose and the control was performed and the results are presented in the last column of Table VII (2.3.1.2.). The resulting P-values further support the assertion of the no statistically significant tumor trend. Thus, the overall conclusion is:

The results provide no evidence of a statistically significant dose related tumor trend.

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3.3.3. Validity of Study Design

The following criteria are frequently used for the validity of a carcinogenicity study:

i. There should be enough animals exposed, for a long enough period of time, to allow for of late developing tumers.

ii. The dose levels should be high enough to give animals reasonable chance of developing tumors.

Concerning the first issue, for a two year study, there should at least 50% survival between weeks 80-90, in the high dose group. As can be seen from Table II (2.3.1.1.) and Table V (2.3.2.1.), for the 125 mg/kg/day dose, there were 35 (70%) male and 38 (76%) female rats still alive at the begining of Week 92. With respect to the second issue, as stated in the submission, the doses of 2, 25, and 125 mg/kg/day are at least 10, 125, and 625 fold the single human dose of 0.2 mg/kg (In a

communication with Dr. Steele, the adequacy of the level of doses was confirmed).

Conclusion: The validity of the design for the Rat Study is demonstrated.

3. MOUSE STUDY

3.1. Design, Clinical and Statistical Procedures

3.1.1. Design and its Validity

This is a 100-week study on CD-1 male and female mice with the objective of assessing the oncogenic/carcinogenic potential of MAXALT. There were four treatment groups consisting of a control and MAXALT doses at 2, 25, and 125 mg/kg/day. There were 100 animals in the control and 50 in each MAXALT treatment group.

3.1.2. Clinical Procedures

During the study, the mice were observed daily for mortality and weekly for clinical signs. Ophthalmic examinations were conducted at the beginning of the study and during Weeks 53 and 93 on all surviving animals. A complete necropsy was performed on all animals, whether dying spontaneously, killed due to poor physical condition, or were terminally sacrificed, except those necropsied and replaced for causes unrelated to treatment during the first several weeks of the study.

The terminal sacrifice for the male and female mice started at week 99 and also ended at week 100.

3.1.2. Statistical Procedures

Similar to the rat study, the statistical test for survival is conducted at $\alpha = 0.05$. The statistical test for the incidences of the various type of tumors was performed at $\alpha = 0.05$ with the adjustment for multiple testing (see footnote 3, page 5).

3.2. Sponsor's Results and Conclusion

The sponsor's analyses include mortality and tumors trend analysis. The results are summarized below:

3.2.1. Mortality/Survival Analysis

The following table presents the sponsor's summary of the percent mortality during the study.

Table VIII (3.2.1): Percent (%) of Mortality/Survival During the Study

		Males				Females			
		Cont.	2 mg	25 mg	125 mg	Cont.	2 mg	25 mg	125 mg
Mortality/ Survival (%)	Found Dead Up to Week 98	48	22	19	29	52	27	26	26
	Survived at Week 98	52	28	31	21	48	23	24	24
	Total	100	50	50	50	100	50	50	50
	Trend Test P-Value ¤	--	--	--	**0.151**	--	--	--	**0.073**

¤: The P-values resulted from the pairwise log-rank test comparing the doses with the control.

The sponsor's survival analysis consists of sequentially pairwise log-rank tests at $\alpha = 0.05$, comparing mortality in MAXALT doses with that in control. The method proceeds from the high to low dose. From the results, the sponsor concluded that there is no statisticaly significant difference in mortality in the MAXALT 125 mg/kg/day group as compared to the control ($P < 0.05$).

Comment: This reviewer's analysis, which used the log-rank test with inclusion of all treatments in the analysis, also resulted in no statistically significant difference among doses.

3.2.2. Tumor Trend Analysis

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With a similar procedure as for rats, the tumor trend test was performed, separately, for "arithmetic", "Logarithmic" and "Ordinal" scales. The reported P-value was the smallest P-value amongst the three P-values generated by the three analyses (one analysis for each dose scaling). The tests were one-sided at α=0.05; however, extra P-value adjustments were considered for the multiplicity testing (see Footnote 1 and 2). **In conclusion, the sponsor found no significant tumor trend.**
Comment: This reviewer also did not find any statistically significant dose related tumor in his analysis. However, this reviewer used the FDA's Guideline for his evaluation (see Footnote 3).

3.3. Reviewer's Analysis and Conclusion

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The analyses performed for the male and female mice are exactly the same (similarly for the male and female mice). However, a separate discussion will be presented for males and females.

The analyses consist:

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1. Mortality/survival analyses which consist: (i) Kaplan-Meier estimate of the survival Function; (ii) Dose-Mortality Trend Test, using both Cox Regression and Non-Parametric Kruskal-Wallis methods. The analysis was conducted with all treatments included as well as for the pairwise comparison between the high dose and the control.

2. Organ-tumor trend analysis, according to the Peto's method (see Footnote 4), adjusts for posible differences in survival between the groups by partitioning the 100 weeks into the sub-intervals of 0-49, 50-74, 75-89, 90-98, 99-100. The analysis presents the Exact as well as the Asymptotic P-values for the dose related organ-tumor trend. The detailed results of the analyses are presented in **Appendix C (Male-Mice)** and **Appendix D (Female-Mice)**.

Comments: (i) There are substantial differences between the **Exact** and **Asymptotic** P-values for the cases that there were very small incidences of tumors, such as one or two animals with the tumor in the high dose. For such cases, the use of asymptotic results is inappropriate and therefore, this reviewer uses the exact P-values for his evaluation. (ii) Overall, there was no statistically significant dose related organ-tumor trend;- however, there were cases where **P > 0.025** for exact, but **P < 0.025** for the asymptotic P-values. Although, the exact p-values should be used for the conclusion, however, for the purpose of not omitting any noticeable findings, those cases were extracted from the Appendix C (Male-Mice) and Appendix D (Female-Mice) and are displayed in a table in the main body of this review.

3.3.1. Male Mice

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3.3.1.1. Mortality/Survival Analysis

Table IX (3.3.1.1) displays the distribution of the number and the percent of the male mice which either died during the weeks 1 to 98 or were terminally sacrificed during the week 99.

TABLE IX (3.3.1.1.) Distribution of Number of Male Mice Died or Terminally Sacrificed

Week	Control			2 mg/kg/day			25 mg/kg/day			125 mg/kg/day			No. Died Total
	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	
0-49	100	6	6.0	50	3	6.0	50	4	8.0	50	4	8.0	17
50-74	94	9	9.0	47	4	8.0	46	2	4.0	46	7	14.0	22
75-89	85	16	16.0	43	8	16.0	44	7	14.0	39	8	16.0	39
90-98	69	15	15.0	35	7	14.0	37	6	12.0	31	10	20.0	38
Terminal■ Sacrifice	54	54	54.0	28	28	56.0	31	31	62.0	21	21	42.0	134

■: The number of animals terminally sacrificed is the same as the number of animals survived after week 98.

The comparisons among doses, with respect to the % of animals died, show no evidence of a dose related mortality trend. This also can be seen from **Figure V (3.3.1.1.)** which displays the cumulative distribution of the percent of mice death and from **Figure VI (3.3.1.1.)**, the Kaplan-Meier estimates of the survival function.

FIGURE V (2.3.1.1.) Cumulative Distribution of Percent of Male Mice Died During the Study

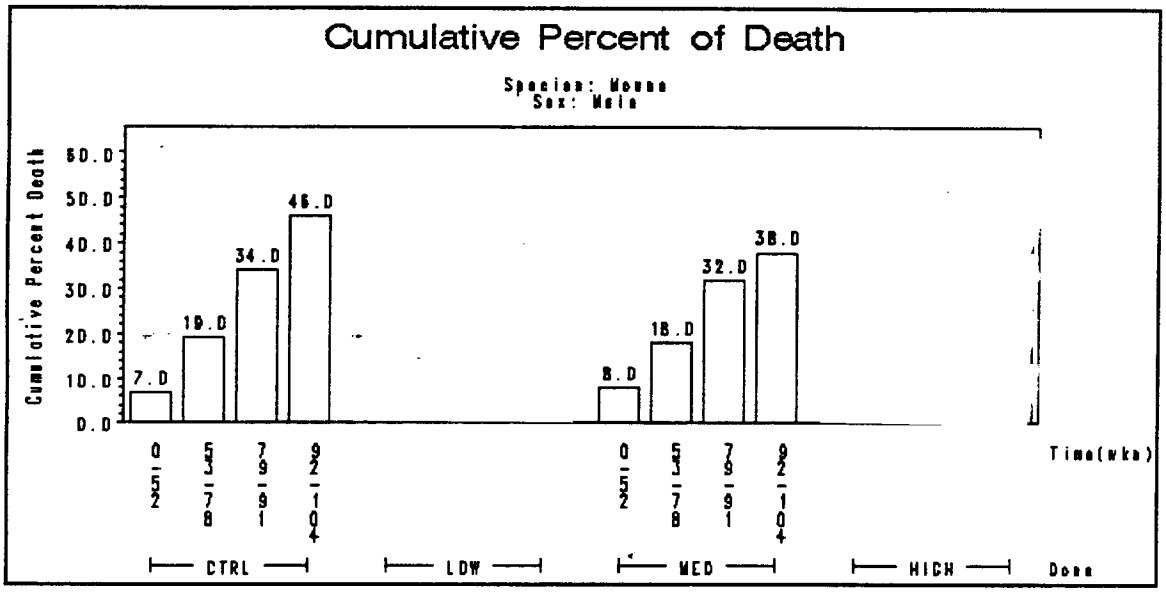

FIGURE VI (3.3.1.1.) Kaplan-Meier Estimate of the Survival Function for the Male Mice

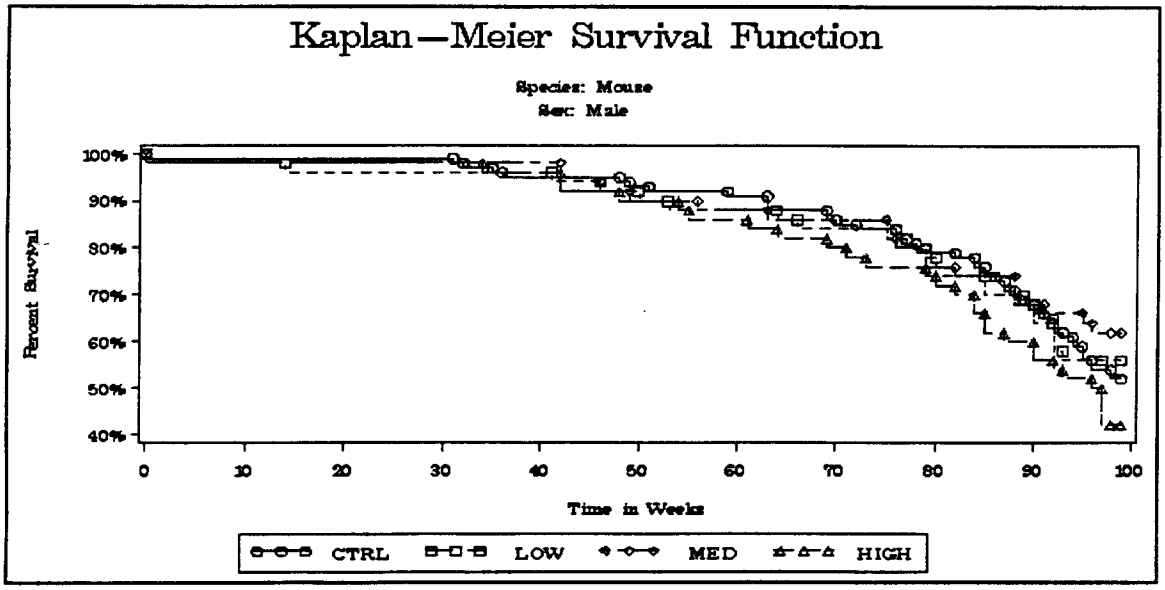

Figure IV (2.3.2.1.) shows the homogeneity of the survival distributions in the 4 treatment groups.

The results of Cox Regression and Non-Parametric Kruskal-Wallis are summarized in **Table X (3.3.1.1.)**. The results show no evidence of a statistically significant dose related mortality trend (P>0.05).

Comment: This reviewer's results confirm the sponsor's findings.

TABLE X (3.3.1.1.) Dose Related Mortality Trend Test for Male Mice

Method	Time Adjusted Trend-Test	All Treatments Included		High Dose vs Control	
		Statistics	P-Value	Statistics	P-Value
Cox	Dose-Mortality Trend	2.46	0.1167	1.48	0.2232
	Departure From Trend	1.28	0.5276	--	--
	Homogeneity	3.74	0.2910	--	--
Kruskal-Wallis	Dose-Mortality Trend	2.15	0.1429	1.66	0.1971
	Departure From Trend	0.95	0.6209	--	--
	Homogeneity	3.10	0.3765	--	--

2.3.1.2. Tumor Trend Analysis

Overall, the results have not shown any statistically significant dose related trend for the observed organ-tumor cases. By reading through **Table I.C (Male-Mice)** of Appendix C (Male-Mice), there were three cases that analysis resulted in **P = 0.0120** for the asymptotic but P = 0.1567 for the exact P-values. Those are summarized in **Table XI (3.3.1.2.).**

TABLE XI (3.3.1.2.): Somewhat Noticeable Tumor Trends in Male Mice

ORGAN TYPE	TUMOR TYPE	Number of Incidences Per Treatment				Incidental or Fatal	Rare or Common ¤	Trend Analysis P-Values		125 mg vs Control Exact P-Value
		Cont	2 mg	25 mg	125 mg			Exact	Asymp-totic	
Pancreas Islet	Adenoma	0	0	0	1	IN	R	0.1567	0.0120	0.2800
Peritoneum	Adenoma	0	0	0	1	IN	R	0.1567	0.0120	0.2800
Skin	Fibroma	0	0	0	1	IN	R	0.1567	0.0120	0.2800

¤ : Considered as a common tumor if the incidental rate is > 1% historically or in Control Group.

Using the FDA's criteria (see Footnote 3) and the Exact P-values, the trends for these organ-tumor cases are not statistically significant.

A pairwise comparison between the high dose and the control was performed and the results are presented in the last column of Table XI (3.3.1.2.). The resulting P-values further support the assertion of no statistically significant tumor trend. Thus, the overall conclusion is:

The results provide no evidence of a statistically significant dose related tumor trend.

3.3.1. Female Mice
3.3.1.1. Mortality/Survival Analysis

Table XII (3.3.1.1) displays the distribution of the number and the percent of the female mice which either died during the weeks 1 to 98 or were terminally sacrificed during the week 99.

TABLE XII (3.3.1.1.) Distribution of Number of Female Mice Died or Terminally Sacrificed

Week	Control			2 mg/kg/day			25 mg/kg/day			125 mg/kg/day			No. Died Total
	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	No. At Risk	No. Died	% Died	
0-49	100	5	5.0	50	3	6.0	50	3	6.0	50	3	6.0	14
50-74	95	14	14.0	47	7	14.0	47	5	10.0	47	8	16.0	34
75-89	81	22	22.0	40	9	18.0	42	11	22.0	39	5	10.0	47
90-98	59	10	10.0	31	7	14.0	31	7	14.0	34	5	10.0	29
Terminal■ Sacrifice	49	49	49.0	24	24	48.0	24	24	48.0	29	29	58.0	126

■: The number of animals terminally sacrificed is the same as the number of animals survived after week 98.

The comparisons among doses, with respect to the % of animals died, show no evidence of a dose related mortality trend. This can be seen also from **Figure VII (3.3.1.1.)** which displays the cumulative distribution of the percent of mice death and from Figure **VIII (3.3.1.1.)**, the Kaplan-Meier estimates of the survival function.

FIGURE V II (3.3.1.1.) Cumulative Distribution of Percent of Female Mice Died During the Study

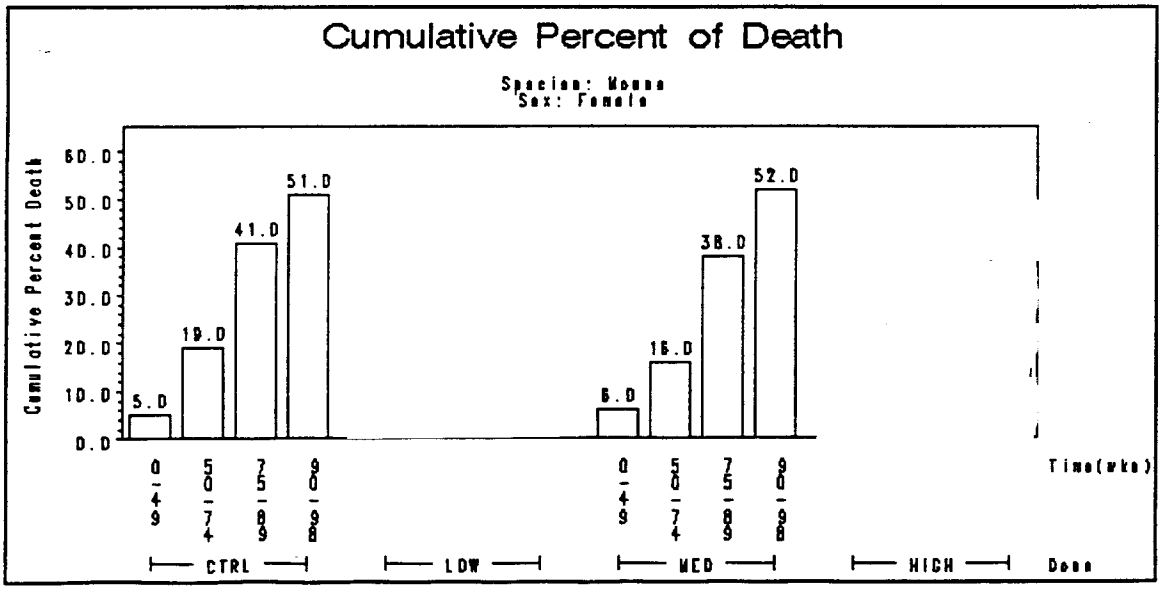

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FIGURE VIII (3.3.1.1.) Kaplan-Meier Estimate of the Survival Function for the Female Mice

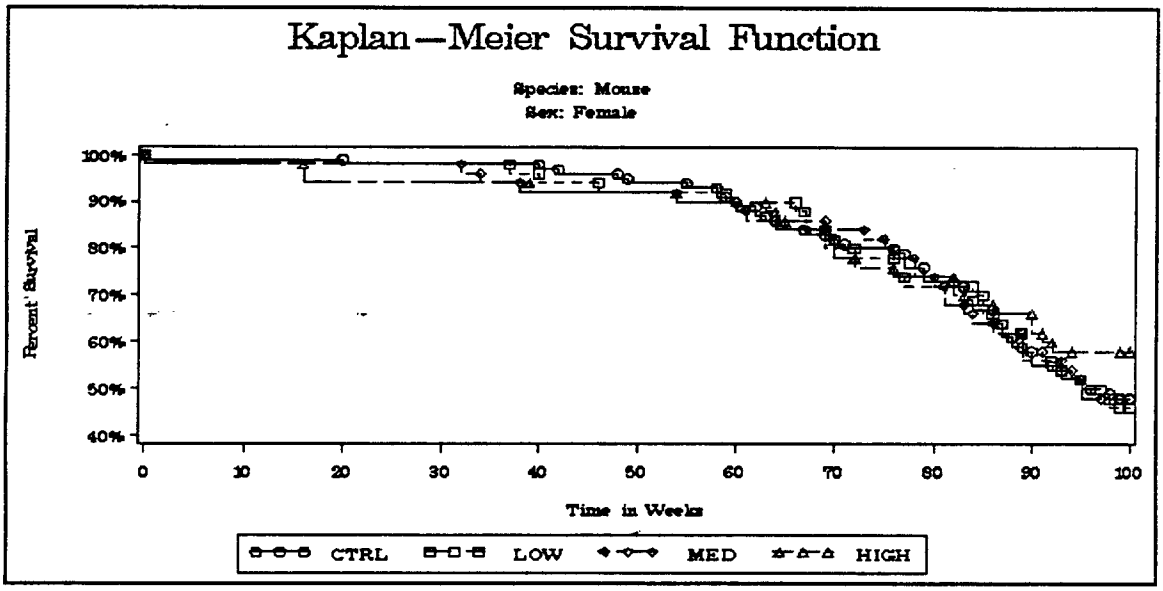

Figure VIII (3.3.1.1.) shows the homogeneity of the survival distributions in the 4 treatment groups.

The results of Cox Regression and Non-Parametric Kruskal-Wallis are summarized in **Table XIII (3.3.1.1.)**. The results show no evidence of a statistically significant dose related mortality trend (P>0.05).

Comment: This reviewer's results confirm the sponsor's findings.

TABLE XIII (3.3.1.1.) Dose Related Mortality Trend Test for Female Mice

Method	Time Adjusted Trend-Test	All Treatments Included		High Dose vs Control	
		Statistics	P-Value	Statistics	P-Value
Cox	Dose-Mortality Trend	0.85	0.3571	0.53	0.4676
	Departure From Trend	0.07	0.9664	--	--
	Homogeneity	0.92	0.8215	--	--
Kruskal-Wallis	Dose-Mortality Trend	0.47	0.4945	0.44	0.5069
	Departure From Trend	0.04	0.9800	--	--
	Homogeneity	0.51	0.9173	--	--

2.3.1.2. Tumor Trend Analysis

Overall, the results show no evidence of a statistically significant dose related tumor trend for the observed organ-tumor cases. By reading through Table I.D (Female-Mice), there are two cases were the P > 0.025 for the exact and P < 0.025 for the asymptotic P-values. These cases are presented in **Table XIV (3.3.1.2.).**

TABLE XIV (3.3.1.2.): Somewhat Noticeable Tumor Trends in Female Mice

ORGAN TYPE	TUMOR TYPE	Number of Incidences Per Treatment				Incidental or Fatal	Rare or Common ¤	Trend Analysis P-Values		125 mg vs Control Exact P-Value
		Cont	2 mg	25 mg	125 mg			Exact	Asymp-totic	
Spleen	Hemangioma	0	0	0	1	IN	R	0.0516	0.0054	
Vaginal Cervix	Sarcoma	0	0	0	1	FA	R	0.1724	0.0163	

¤ : Considered as a common tumor if the incidental rate is > 1% historically or in Control Group.

Using the FDA's criteria (see Footnote 3) and the Exact P-values, the trends for these organ-tumor cases are not statistically significant.

A pairwise comparison between the high dose and the control was performed and the results are presented in the last column of Table XIV (3.3.1.2.). The resulting P-values further support the assertion of no statistically significant tumor trend. Thus, the overall conclusion is:

The results provide no evidence of a statistically significant dose related tumor trend.

3.3.3. Validity of Study Design:

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The following criteria are frequently used for the validity of a carcinogenicity study:

i. There should be enough animals exposed, for a long enough period of time, to allow for of late developing tumers.

ii. The dose levels should be high enough to give animals reasonable chance of developing tumors.

Concerning the first issue, for a two year study, there should at least 50% survival between weeks 80-90, in the high dose group. As can be seen from Table IX (3.3.1.1.) and Table XII (3.3.2.1.), for the 125 mg/kg/day dose there were 31 (62%) male and 34 (68%) female mice still alive at the begining of Week 90. With respect to the second issue, as stated in the submission, the doses of 2, 25, and 125 mg/kg/day are at least 10, 125, and 625 fold the single human dose of 0.2 mg/kg (In a communication with Dr. Steele, the adequacy of the level of doses was confirmed).

Conclusion: The validity of the design for the Rat Study is demonstrated.

4. REVIEWER'S CONCLUSION

Overall,

- For both the male and female rats, there was no evidence of a statistically significant treatment related mortality trend.
- For both the male and female rats, there was no evidence of a statistically significant treatment related organ-tumor trend.
- For both the male and female mice, there was no evidence of a statistically significant treatment related mortality trend.
- For both the male and female mice, there was no evidence of a statistically significant treatment related organ-tumor trend.

/S/

Kooros Mahjoob, Ph.D.
Mathematical Statistician

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Concur:

Dr. Sahlroot /S/ 4/6/98

Dr. Chi /S/ 4/8/98

This review consists of 20 pages which includs text, 14 tables and 8 Figures. There are 4 appendices attached in the back (Appendix A (Male Rats), 5 pages; Appendix B (Female Rats), 6 pages; Appendix C (Male Mice), 5 pages; and Appendix D (Female Mice), 7 pages.

CC:

Arch. NDA 20-864/Rizatriptan Benzoate (MAXALT®).

HFD-120
HFD-120/Dr. Fitzgerald
HFD-120/Dr. Steele
HFD-120/ Mrs. Chen
HFD-344/Dr. Barton
HFD-700/Dr. Fairweather
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710)/Mrs. Kelly
HFD-710/Dr. Mahjoob
HFD-710/Chron.

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K. Mahjoob: 4-5301:Biometrics 1/Team 1:km.

Statistical Reviewer: Kooros Mahjoob

APPENDIX A (Male-Rats)

NDA 20-864 MAXALT

Analysis of Carcinogenic Potential in Male Rats
Test of Dose-Response (Tumor) Positive Linear Trend

Program Author: Ted Guo, PH.D, CDER/FDA

Note:

- Dose Levels Included: CTRL LOW MED HIGH (0 2 25 125)
- Missing value in Tumor-Caused Death is treated as tumor not causing death
- Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

TABLE I.A (Male-Rats):

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TYPES	TIME STRATA	ROW NO.	2xC CONTINGENCY -----TABLE-----	EXACT PROB =PR(STATISTIC.GE.OBSERVED)	ASYMP TOTIC	ASYMP(CONTI NUITY CORR)
LIVER	(14000)	IN	92-104	1	0 1	0.4229	0.2809	0.2819
HEPATOCELLULAR ADENOMA	(1660)	IN	92-104	2	5 8			
		IN	105-105	1	4 2			
		IN	105-105	2	63 24			
Spontaneous tumor rate 4%	in ctrl. -	Total		-	4 3			
LIVER	(14000)	IN	92-104	1	0 1	0.5700	0.4610	0.4620
HEPATOCELLULAR CARCINOMA	(1670)	IN	92-104	2	5 8			
		IN	105-105	1	11 4			
		IN	105-105	2	56 22			
Spontaneous tumor rate 11%	in ctrl. -	Total		-	11 5			
PANCREAS ISLET	(18073)	IN	92-104	1	0 2	0.0432	0.0226	0.0227
ADENOMA	(70)	IN	92-104	2	5 7			
		IN	105-105	1	10 8			
		IN	105-105	2	57 18			
Spontaneous tumor rate 10%	in ctrl. -	Total		-	10 10			
ADRENAL	(22000)	IN	79-91	1	0 1	0.9018	0.7894	0.7902
PHEOCHROMOCYTOMA	(3060)	IN	79-91	2	15 4			
		IN	105-105	1	6 0			
		IN	105-105	2	61 26			
Spontaneous tumor rate 6%	in ctrl. -	Total		-	6 1			
ADRENAL CORTEX	(22080)	IN	105-105	1	2 0	1.0000	0.8122	0.8138
ADENOMA	(70)	IN	105-105	2	65 26			
Spontaneous tumor rate 2%	in ctrl. -	Total		-	2 0			
PARATHYROID	(27000)	IN	79-91	1	0 1	0.7321	0.4341	0.4365
ADENOMA	(70)	IN	79-91	2	15 4			
		IN	92-104	1	1 0			
		IN	92-104	2	4 9			
Spontaneous tumor rate LE 1%	in ctrl. -	Total		-	1 1			

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PITUITARY	(29000)	IN	53-78	1	1	1	0.1681 0.1304 0.1306
ADENOMA	(70)	IN	53-78	2	3	3	
		IN	79-91	1	2	1	
		IN	79-91	2	9	2	
		IN	92-104	1	2	1	
		IN	92-104	2	3	6	
		IN	105-105	1	27	11	
		IN	105-105	2	40	15	
		FA	58	1	0	1	
		FA	58	2	93	46	
		FA	75	1	1	0	
		FA	75	2	90	46	
		FA	77	1	0	2	
		FA	77	2	89	43	
		FA	78	1	1	1	
		FA	78	2	87	41	
		FA	80	1	1	0	
		FA	80	2	84	40	
		FA	83	1	1	0	
		FA	83	2	82	40	
		FA	87	1	2	0	
		FA	87	2	77	37	
		FA	91	1	0	2	
		FA	91	2	72	35	
		FA	95	1	0	1	
		FA	95	2	70	34	
		FA	99	1	0	1	
		FA	99	2	68	29	
Spontaneous tumor rate 38% in ctrl. - Total				-	38	22	
THYROID PARAFOLLICULAR CE	(31099)	IN	92-104	1	0	1	0.8681 0.7025 0.7041
CARCINOMA	(410)	IN	92-104	2	5	8	
		IN	105-105	1	3	0	
		IN	105-105	2	64	26	
Spontaneous tumor rate 3% in ctrl. - Total				-	3	1	
THYROID PARAFOLLICULAR CE	(31099)	IN	79-91	1	1	0	0.9754 0.9199 0.9203
ADENOMA	(70)	IN	79-91	2	14	5	
		IN	92-104	1	1	0	
		IN	92-104	2	4	9	
		IN	105-105	1	6	1	
		IN	105-105	2	61	25	
Spontaneous tumor rate 8% in ctrl. - Total				-	8	1	
THYROID FOLLICULAR CELL	(31413)	IN	79-91	1	0	1	0.4597 0.2253 0.2273
CARCINOMA	(410)	IN	79-91	2	15	4	
		IN	105-105	1	1	0	
		IN	105-105	2	66	26	
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	1	
TESTIS	(49000)	IN	105-105	1	1	0	1.0000 0.7334 0.7363
HEMANGIOMA	(1570)	IN	105-105	2	66	26	
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0	
TESTIS	(49000)	IN	92-104	1	0	1	0.3890 0.2701 0.2711
INTERSTITIAL CELL TUMOR	(1910)	IN	92-104	2	5	8	
		IN	105-105	1	6	3	
		IN	105-105	2	61	23	
Spontaneous tumor rate 6% in ctrl. - Total				-	6	4	
TESTIS	(49000)	IN	105-105	1	1	0	1.0000 0.7334 0.7363
MESOTHELIOMA	(2300)	IN	105-105	2	66	26	
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0	
PROSTATE	(51000)	FA	88	1	1	0	1.0000 0.7574 0.7600
ADENOCARCINOMA	(60)	FA	88	2	75	37	
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0	
SKIN	(59000)	IN	105-105	1	2	2	0.4470 0.2865 0.2880

FIBROMA	(1330)	IN	105-105	2	65	24		
		FA	87	1	1	0		
		FA	87	2	78	37		
Spontaneous tumor rate 3% in ctrl. - Total				-	3	2		
SKIN	(59000)	IN	105-105	1	1	0	1.0000	0.8214 0.8230
FIBROSARCOMA	(1350)	IN	105-105	2	66	26		
		FA	79	1	1	0		
		FA	79	2	86	40		
Spontaneous tumor rate 2% in ctrl. - Total				-	2	0		
SKIN	(59000)	IN	105-105	1	1	0	1.0000	0.7334 0.7363
LIPOMA	(2080)	IN	105-105	2	66	26		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
SKIN	(59000)	IN	105-105	1	1	0	1.0000	0.7334 0.7363
MAST CELL SARCOMA	(2180)	IN	105-105	2	66	26		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
SKIN	(59000)	IN	53-78	1	1	0	1.0000	0.8759 0.8775
BASAL CELL TUMOR	(280)	IN	53-78	2	5	8		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
SKIN	(59000)	IN	105-105	1	1	0	1.0000	0.7334 0.7363
PAPILLOMA	(2910)	IN	105-105	2	66	26		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
SKIN SEBACEOUS GLAND	(59173)	IN	105-105	1	0	1	0.2796	0.0542 0.0552
ADENOMA	(70)	IN	105-105	2	67	25		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	1		
MAMMARY GLAND	(61000)	IN	105-105	1	1	0	1.0000	0.7334 0.7363
ADENOCARCINOMA	(60)	IN	105-105	2	66	26		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
LUNG	(71000)	IN	105-105	1	1	0	1.0000	0.7334 0.7363
ADENOCARCINOMA	(60)	IN	105-105	2	66	26		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
LUNG	(71000)	IN	105-105	1	1	0	1.0000	0.7334 0.7363
ADENOMA	(70)	IN	105-105	2	66	26		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
PLEURA	(72000)	FA	99	1	0	1	0.3061	0.0661 0.0672
MESOTHELIOMA	(2300)	FA	99	2	68	29		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	1		
THYMUS	(81000)	IN	105-105	1	1	0	1.0000	0.7334 0.7363
THYMOMA	(3790)	IN	105-105	2	66	26		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
BONE	(84000)	FA	97	1	1	0	1.0000	0.7472 0.7499
OSTEOMA	(2730)	FA	97	2	69	31		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
BONE	(84000)	IN	79-91	1	1	0	1.0000	0.7182 0.7212
CHORDOMA	(581)	IN	79-91	2	14	5		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
SKELETAL MUSCLE	(87000)	FA	93	1	1	0	1.0000	0.7572 0.7599
FIBROSARCOMA	(1350)	FA	93	2	71	35		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
SKELETAL MUSCLE	(87000)	IN	105-105	1	1	0	1.0000	0.7334 0.7363
HEMANGIOSARCOMA	(1580)	IN	105-105	2	66	26		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
SKELETAL MUSCLE	(87000)	IN	105-105	1	1	0	1.0000	0.7334 0.7363
RHABDOMYOSARCOMA	(3420)	IN	105-105	2	66	26		

Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
BRAIN	(89000)	FA	85	1	0	1	0.3193	0.0722 0.0734
GLIOMA	(1468)	FA	85	2	81	37		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	1		
BRAIN	(89000)	FA	47	1	1	0	1.0000	0.7625 0.7651
ASTROCYTOMA	(210)	FA	47	2	95	49		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
STOMACH NONGLANDULAR MUCO	(9027)	IN	79-91	1	0	1	0.2500	0.0417 0.0425
PAPILLOMA	(2910)	IN	79-91	2	15	4		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	0	1		
NERVE	(93000)	FA	61	1	1	0	1.0000	0.7591 0.7617
SCHWANNOMA	(3475)	FA	61	2	92	46		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
EAR ZYMBAL'S GLAND	(97485)	FA	98	1	1	0	1.0000	0.7487 0.7514
CARCINOMA	(410)	FA	98	2	68	31		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
PRIMARY SITE UNDETERMINED	(98000)	IN	105-105	1	0	1	0.2799	0.1612 0.1619
HISTIOCYTIC SARCOMA	(1715)	IN	105-105	2	67	25		
		FA	79	1	1	0		
		FA	79	2	86	40		
		FA	90	1	2	0		
		FA	90	2	72	37		
		FA	95	1	0	1		
		FA	95	2	70	34		
		FA	101	1	0	1		
		FA	101	2	68	26		
Spontaneous tumor rate 3% in ctrl. - Total				-	3	3		
PRIMARY SITE UNDETERMINED	(98000)	FA	80	1	1	0	1.0000	0.7537 0.7563
LEUKEMIA	(2050)	FA	80	2	84	40		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		
PRIMARY SITE UNDETERMINED	(98000)	FA	84	1	1	0	1.0000	0.7548 0.7575
LYMPHOMA	(2150)	FA	84	2	81	39		
Spontaneous tumor rate LE 1% in ctrl. - Total				-	1	0		

- 4 - (End of File)

APPEARS THIS WAY
ON ORIGINAL

APPENDIX A (Male-Rats)

NDA 20-864 MAXALT

Analysis of Carcinogenic Potential in Male Rats
Test of Dose-Response (Tumor) Positive Linear Trend

TABLE II.A (Male-Rats): Summary of Table I.A (Male-Rats)

Organ Code	Organ Name	Tumor Code	Tumor Name	Exact-P	Asymp-P	AsyCor-P
18073	PANCREAS ISLET	70	ADENOMA	0.0432	0.0226	0.0227
29000	PITUITARY	70	ADENOMA	0.1681.	0.1304	0.1306
9027	STOMACH NONGLANDULAR MUCO	2910	PAPILLOMA	0.2500	0.0417	0.0425
59173	SKIN SEBACEOUS GLAND	70	ADENOMA	0.2796	0.0542	0.0552
98000	PRIMARY SITE UNDETERMINED	1715	HISTIOCYTIC SARCOMA	0.2799	0.1612	0.1619
72000	PLEURA	2300	MESOTHELIOMA	0.3061	0.0661	0.0672
89000	BRAIN	1468	GLIOMA	0.3193	0.0722	0.0734
49000	TESTIS	1910	INTERSTITIAL CELL TUMOR	0.3890	0.2701	0.2711
14000	LIVER	1660	HEPATOCELLULAR ADENOMA	0.4229	0.2809	0.2819
59000	SKIN	1330	FIBROMA	0.4470	0.2865	0.2880
31413	THYROID FOLLICULAR CELL	410	CARCINOMA	0.4597	0.2253	0.2273
14000	LIVER	1670	HEPATOCELLULAR CARCINOMA	0.5700	0.4610	0.4620
27000	PARATHYROID	70	ADENOMA	0.7321	0.4341	0.4365
31099	THYROID PARAFOLLICULAR CE	410	CARCINOMA	0.8681	0.7025	0.7041
22000	ADRENAL	3060	PHEOCHROMOCYTOMA	0.9018	0.7894	0.7902
31099	THYROID PARAFOLLICULAR CE	70	ADENOMA	0.9754	0.9199	0.9203
22080	ADRENAL CORTEX	70	ADENOMA	1.0000	0.8122	0.8138
84000	BONE	581	CHORDOMA	1.0000	0.7182	0.7212
84000	BONE	2730	OSTEOMA	1.0000	0.7472	0.7499
89000	BRAIN	210	ASTROCYTOMA	1.0000	0.7625	0.7651
97485	EAR ZYMBAL'S GLAND	410	CARCINOMA	1.0000	0.7487	0.7514
71000	LUNG	60	ADENOCARCINOMA	1.0000	0.7334	0.7363
71000	LUNG	70	ADENOMA	1.0000	0.7334	0.7363
61000	MAMMARY GLAND	60	ADENOCARCINOMA	1.0000	0.7334	0.7363
93060	NERVE	3475	SCHWANNOMA	1.0000	0.7591	0.7617
98000	PRIMARY SITE UNDETERMINED	2050	LEUKEMIA	1.0000	0.7537	0.7563
98000	PRIMARY SITE UNDETERMINED	2150	LYMPHOMA	1.0000	0.7548	0.7575
51000	PROSTATE	60	ADENOCARCINOMA	1.0000	0.7574	0.7600
87000	SKELETAL MUSCLE	1350	FIBROSARCOMA	1.0000	0.7572	0.7599
87000	SKELETAL MUSCLE	1580	HEMANGIOSARCOMA	1.0000	0.7334	0.7363
87000	SKELETAL MUSCLE	3420	RHABDOMYOSARCOMA	1.0000	0.7334	0.7363
59000	SKIN	280	BASAL CELL TUMOR	1.0000	0.8759	0.8775
59000	SKIN	1350	FIBROSARCOMA	1.0000	0.8214	0.8230
59000	SKIN	2080	LIPOMA	1.0000	0.7334	0.7363
59000	SKIN	2180	MAST CELL SARCOMA	1.0000	0.7334	0.7363
59000	SKIN	2910	PAPILLOMA	1.0000	0.7334	0.7363
49000	TESTIS	1570	HEMANGIOMA	1.0000	0.7334	0.7363
49000	TESTIS	2300	MESOTHELIOMA	1.0000	0.7334	0.7363
81000	THYMUS	3790	THYMOMA	1.0000	0.7334	0.7363